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Dr Macdonald Brown
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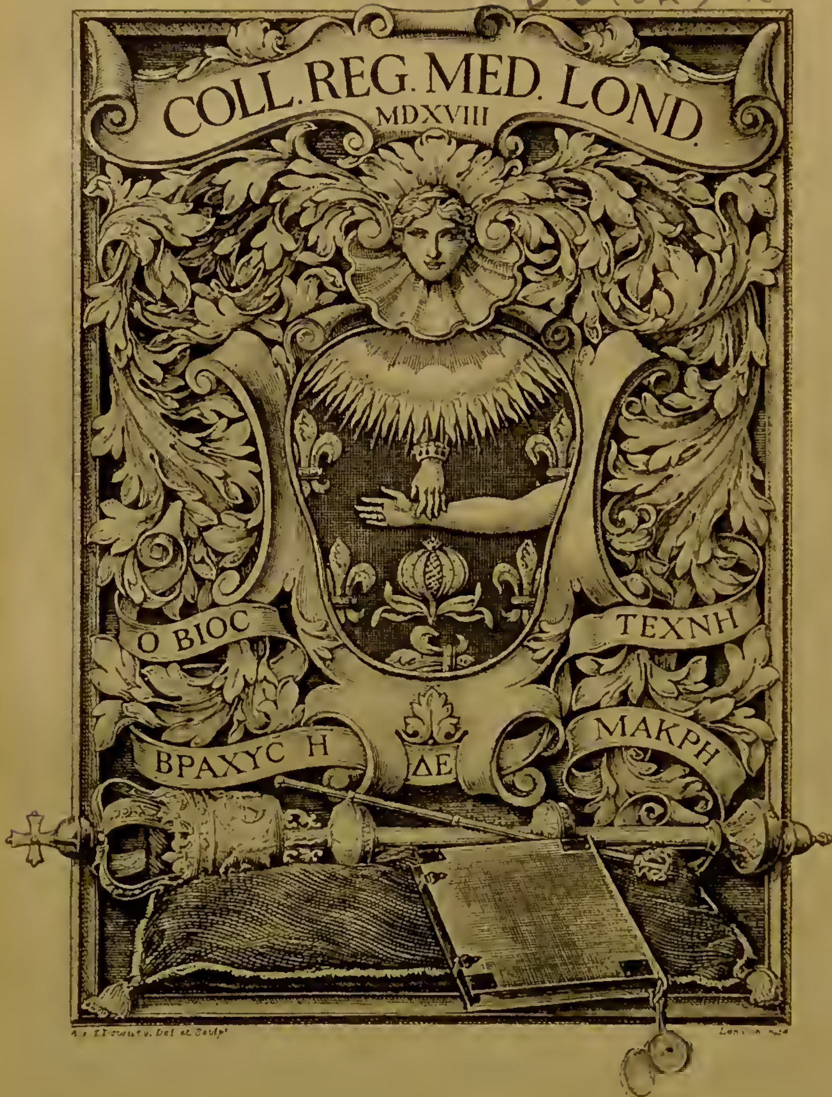
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PHARMACOLOGY, THERAPEUTICS

AND

MATERIA MEDICA

Macdonald Brown

A TEXT-BOOK

OF

PHARMACOLOGY, THERAPEUTICS

AND

MATERIA MEDICA

BY

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ADAPTED TO THE

United States Pharmacopoeia

BY

FRANCIS H. WILLIAMS, M.D. Boston, Mass.

THIRD EDITION

CONTAINING THE

ADDITIONS (1891) *TO THE BRITISH PHARMACOPŒIA*

London

MACMILLAN AND CO.

AND NEW YORK

1893

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Additions (1891) *to the British Pharmacopœia. Reprinted November* 1891, 1893.

TO

The Memory of

SIR ROBERT CHRISTISON, BART. &c.

HIS HONOURED TEACHER

AND TO

CARL LUDWIG

HIS BELOVED MASTER

THIS BOOK IS GRATEFULLY DEDICATED

BY

THE AUTHOR

PREFACE

TO

THE THIRD EDITION.

The rapid exhaustion of the second edition of this work has prevented me from making as many improvements in the present edition as I could have desired. At the same time I have tried, as far as the short time at my disposal would allow, to amend the imperfections of former editions, as well as to bring the work up to date and render it more useful by the introduction of new matter.

The treatment of one of the most important portions of Pharmacology, viz. the Connection between Chemical Constitution and Physiological Action, is still very meagre, because I find that the size of this work would be too much increased were I to treat the subject fully, and I am therefore preparing a small text-book upon it.

The struggle for existence between microbes and the living organism, which in the first edition was only illustrated by a single diagram of a bacillus and amœba, is now fully illustrated by woodcuts copied from Metschnikoff's paper. The views of Hughlings Jackson on the nervous system have been illustrated by a diagram which, when covered with successive layers of thin and semi-transparent paper, exhibits the effect of anæsthetics and narcotics in successively abolishing various faculties. The recent work of Kühne and Politzer on the mode of action of curare has been noticed, and the pathology of tremor discussed. The section on the action of drugs upon the eye has been carefully revised. The section on antipyretics has been rendered somewhat fuller, and some diagrams illustrating the pathology of fever and the mode of action of antipyretics have been introduced; but it is very difficult in the present state of our knowledge to deal satisfactorily with this subject. Paragraphs on the

treatment of cough and on the pathology and treatment of asthma have been introduced. The researches of Adami on diuretics have been noticed, but they have not necessitated any essential change in the text, as the communication between the portal vein of the kidney and the renal artery had been already allowed for in describing Nussbaum's researches in the first edition. The views expressed in the first edition regarding the mode of action of caffeine have been confirmed and extended by the observations of Schroeder and Munk. The researches of Jendràssik on the diuretic action of calomel and the explanation advanced by Locke have been noticed.

The arrangement of the Vegetable Materia Medica has been almost entirely remodelled on Hooker's plan, and a short introduction has been added to it, in which I have tried to show the use of botanical arrangement, as well as to protest against the abuse of it in the examination of students in Materia Medica.

By the use of small type for matters which are of practically little interest to general students, and yet are occasionally wanted for reference, a certain amount of space has been gained, at the same time that the general student is enabled at a glance to distinguish the parts which are of little or no interest to him. Notwithstanding my efforts to condense it, the present edition contains about 120 pages more than the second, but by using thinner paper the bulk of the volume has been little, if at all, increased.

The General Index has been carefully revised. The Index of Diseases and Remedies has been revised to a certain extent, but it still remains a mere skeleton of what it ought to be. It is little more than a list of drugs which have been recommended by somebody or other at some time or other in the treatment of certain diseases. In a few instances the conditions supposed to indicate the use of one drug in preference to another have been given, but I have not yet been able to sift the statements which have been made regarding the different drugs. The only use of the Index at present is simply to remind the practitioner who is treating a disease of the names of drugs which have been proposed as remedies for it. Thus, under the head of Hydrophobia I have mentioned a number of remedies which have been used or proposed, because those who may have to treat a case of this disease may wish to try some remedy, although my own experience leads me to think that almost all well-marked cases will have a fatal issue whatever the drugs employed may be.

The idea of a Therapeutic Index was taken from that in Ringer's 'Therapeutics,' and I wished to make one still more full and complete by comparing his index with those of Bartholow and H. C. Wood, with Waring's 'Therapeutics,' and with the wonderful 'Medical Digest' of Dr. Neale. After I had begun to do this, I found that a similar idea had occurred to Dr. S. O. L. Potter, who had already published an index of 'Comparative Therapeutics,' in which he gave a list of remedies taken from the works of Aitken, Bartholow, Niemeyer, Phillips, Piffard, Ringer, Stillé, Tanner, Trousseau, H. C. Wood, Waring, and some others. After finding that Dr. Potter had already compared together more works than I expected to do, I used his list, along with Naphey's 'Medical Therapeutics' and Neale's 'Medical Digest,' in preparing my Index. I was unable, however, even with the aid of these works, to make the Index anything more than a mere list of names, excepting in a few instances. So imperfect was it, indeed, that up to the last moment I intended to cancel it, and would have done so had not a case occurred in my own practice which showed me that even a mere list of drugs may sometimes be desirable. I was not unmindful of the old adage that 'Fools and children should not see half-done things,' but I felt confident that the majority of my readers would not belong to either of these classes, and so I allowed the Index to remain. My intention to cancel it, however, led me to omit an acknowledgment of my indebtedness to Dr. Potter, and I have pleasure in acknowledging it now.

My use of Dr. Potter's book has led me to include in the Therapeutic Index one remedy which the homœopaths claim as theirs. His book contains a list of remedies taken from homœopathic works as well as from those I have already named. The two classes of remedies are kept apart in different columns; but I find that, in one instance at least, the amanuensis whom I employed to copy out a number of the drugs from Dr. Potter's book has made a mistake in the column, and has taken 'Apis' as a remedy for tonsillitis from the Homœopathic column. To the best of my knowledge this is the only remedy I have taken from a homœopathic source. If any other remedies claimed as 'homœopathic' have been introduced, they have, I think, been copied from the works of one or other of the authors already mentioned, and in Dr. Phillips's work there are some remedies mentioned without references. But as I intended up to the last moment to cancel the whole list, my revision of it was hasty and

imperfect; and as I omitted to expurgate 'Apis,' I may also possibly have overlooked other remedies. If any such omission has occurred I am sincerely sorry, and I can assure the homœopaths that it is perfectly unintentional.

Perhaps it may be well to take this opportunity of saying a few words in regard to homœopathic remedies and homœopathy generally.

The mere fact that a drug in small doses will cure a disease exhibiting symptoms similar to those produced by a large dose of the drug does not constitute it a homœopathic medicine, for this rule was known to Hippocrates, and the rule *similia similibus curantur* was recognised by him as true in some instances. But Hippocrates was not a homœopath, and he recognised the fact that, while this rule was sometimes true, it was not invariably so.

It seems to me that, in founding the system of homœopathy, Hahnemann has proceeded with his facts as he did with his medicines—diluting his active drugs with inert matter, and diluting his facts with much nonsense.

In what I am about to say, I may be to some extent open to correction, for I cannot claim to know his doctrines so thoroughly as those who believe in and follow him. So far, however, as I know his doctrines, it seems to me that they consist in raising the rule *similia similibus curantur* to the rank of a regular law; in claiming a curative power for infinitesimal doses, and in believing that the diminution in the dose of the drug was made up for by the potency conferred upon it through prolonged trituration. It is no doubt true that in some instances the power of a drug may be increased by trituration, inasmuch as fine subdivision either makes it more easily absorbed or alters its chemical composition, as in the case of mercurial compounds, where the prolonged exposure to the air and friction involved in the trituration may greatly increase the power of the drug by oxidising it, and changing it from a mercurous to a mercuric salt. But in both cases the increased activity conferred upon the drug is strictly limited, although it may be great in the case of the salts of mercury. To suppose it to be exerted *ad infinitum* is sheer nonsense, and the absurdity of infinitesimal doses has been so often demonstrated that it is useless to say more about it.

I think one is justified in describing Hahnemann's experiment with cinchona bark as the foundation-stone of his doctrine of homœopathy; for Dr. Nankivell, in his Presidential Address to

the British Homœopathic Congress at Norwich, says, with regard to the action of quinine in ague, that 'it was this very instance of successful empirical treatment, of specific medicinal action, that led Hahnemann first to investigate the actions of drugs on the healthy human frame, and thus to lay the foundation of the most complete and lucid system of scientific therapeutics that the world has yet seen.' But I have shown in the body of this work (p. 52) that, although Hahnemann's observations were in all probability perfectly correct, the conclusions he drew from them were utterly erroneous.

But there is another side to the question which I think it is only fair to consider also. While Hahnemann's theory was certainly bad, there can, I think, be little doubt that he, like Paracelsus and Priessnitz, has done good service to medical practice. Paracelsus gathered information from shepherds, wise women, and quacks of all sorts, and thereby obtained a knowledge of popular remedies, not generally employed by the profession, but which were nevertheless useful.

Priessnitz did not invent the use of cold water as a remedy, for it was known nearly eighteen hundred years before his time. Musa saved the life of Augustus by the cold bath, but, not knowing exactly how and when to employ it, he killed the nephew of the Emperor by it, and such failures brought the treatment by water into discredit. Priessnitz revived it, and now in the use of cold sponging, wet packs, baths and douches we have a powerful means of treating fever and curing disease.

Hahnemann also did good, and the system which he founded has done great service by teaching us the curative power of unaided Nature, the use of diet and regimen in treating disease, and the more than inutility, the actual hurtfulness, of powerful drugs in many instances. The physician is bound to do the very utmost he can for his patient, and his very anxiety has frequently led him to do harm. He has been afraid to leave the cure of disease to Nature, and by the administration of powerful drugs has frequently injured instead of benefited his patient. The use of infinitesimal doses which could not affect the body of the patient one way or the other, but kept the mind of both patient and physician easy, and allowed the *vis medicatrix naturæ* free scope, has helped us to a more perfect knowledge of the natural course of disease. The use of infinitesimal doses has also led to much care being bestowed by those who use them upon diet and regimen. When a physician administered a large dose

of tartar emetic or of salts and senna, he knew that his remedies would produce vomiting or purgation respectively with considerable certainty, whatever the diet or regimen of the patient might be; but the case was quite different with infinitesimal doses. If a patient was being treated with *carbo vegetabilis* in the thirtieth dilution, the utmost care was necessary in regard to his diet, for if he happened to eat a single piece of burned toast at breakfast, he would consume at the one meal as much vegetable charcoal as would, when properly diluted, have served him for medicine during the remainder of his natural life.

Moreover, the homœopathic practice of giving only one drug has tended greatly to diminish the practice of polypharmacy, and the tinctures, powders, and globules they employ show us a good example in regard to the administration of remedies in an agreeable form. But, although this mode of practice may be employed by homœopaths, it is not homœopathic. We are not homœopaths because we use a single drug at a time and give half an ounce of infusion of digitalis to a patient suffering from heart-disease without thinking it necessary to mix it with broom, squill, or spirit of nitrous ether. Nor are we homœopaths because we use 1–50th of a grain of digitalin instead of the infusion of digitalis. Nor are we homœopaths even if we get a manufacturing chemist to make up the digitalin into a globule with a quarter of a grain of sugar of milk instead of with five grains of extract of liquorice. Nor do we become homœopaths merely because we may employ a small dose instead of a large one, and begin with ten drops of the infusion of digitalis instead of half an ounce.

It is not the use of a single drug at a time, of a small dose, of a globule, nor even, as we have already seen, of a drug which may produce symptoms similar to those of the disease, that constitutes homœopathy. The essence of homœopathy, as established by Hahnemann, lies in the infinitesimal dose and the universal application of the rule *similia similibus curantur*. But the infinitesimal doses are so absurd that I believe they have been discarded by many homœopaths. To such men all that remains of homœopathy is the universality of the rule *similia similibus curantur*, and the only difference between them and rational practitioners lies in the fact that the latter regard the rule as only of partial application. At first sight this difference may seem to be only slight, but it is not so in reality; for while the rational practitioner, refusing to be bound by any 'pathy,' whether it be allopathy, antipathy, or homœopathy, seeks to

trace each symptom back to the pathological change which caused it, and, by a knowledge of the action of drugs on each tissue and organ of the body, to counteract these pathological changes, the homœopath professes to be in possession of a rule which will enable him to select the proper remedy in each case by a consideration of the symptoms, without reference to the pathological condition. He may thus dispense with anatomy, physiology, pathology, and pharmacology. All that is necessary is a list of morbid symptoms on the one hand, and a list of the symptoms produced in healthy men by various drugs on the other.

It is the falsity of the claim which homœopathy makes to be in possession, if not of the universal panacea, at least of the only true rule of practice, that makes homœopathy a system of quackery; yet this arrogant claim constitutes the essence of the system, and the man who, leaving Hahnemann and going back to Hippocrates, regards the rule *similia similibus curantur* as only of partial and not of universal application, has no longer any right to call himself a homœopath.

Yet we hear some leading homœopaths say, 'We do not claim any exclusiveness for our method,' [1] and then complain that they are excommunicated by the medical profession. If they have renounced the errors of Hahnemann's system, they ought not to retain its name, but frankly acknowledge their error and return to rational medicine, of which Hippocrates is regarded as the father. As a medical man is bound to do his utmost for the good of his patient, it is obvious that, although he may employ baths or packs as a mode of treatment, he cannot, without becoming untrue to his profession, throw aside all other means of treatment and become a hydropath; nor can he consult on equal terms with those who, either through ignorance or wilful blindness, deny the use of other means of cure and limit themselves to the application of water. What is true of hydropathy is true of homœopathy. I dislike controversy extremely, and should not have taken up so much of the preface with controversial matter had I not been forced to defend myself by the attacks which certain homœopaths have made upon me.

I may now turn to the pleasanter task of acknowledging my indebtedness to many friends who have helped me in the preparation of this edition. In addition to some of those who helped me with former editions, I have to thank Dr. Hughlings

[1] Preface by Richard Hughes to *The Medical Treatment of our Time.* London: Unwin Brothers, Ludgate Hill.

Jackson for assistance in the construction of the diagram which illustrates his views of the nervous system; Mr. W. H. Jessop and Mr. Tweedy for much aid and many suggestions in revising the section on diseases of the eye; and I am especially grateful to my friend, Dr. Thin, who has greatly added to the value of the book by writing an account of the uses of various remedies in skin diseases. I am indebted to Mr. Whitehead, Dr. Halliburton, and especially to Dr. Sidney Martin, for their assistance in passing this edition through the press. To Dr. Martin I am also indebted for many valuable suggestions, and for such an amount of help that, but for him, the preparation of this edition would certainly have been delayed for many months.

T. LAUDER BRUNTON.

March, 1887.

PREFACE

TO

THE FIRST EDITION.

Some apology is required for the long delay in the appearance of this work, for a number of years have now elapsed since it was advertised as being in the press. More than fifteen years ago, I had a work on *Materia Medica* completely written out and ready for the printer. Some time afterwards, all the arrangements had been made for its publication, and in the course of a few weeks it was to have been issued from the press. Just as I was about to send it to the printer, however, I asked for a little delay in order that I might make some improvements and remove some redundancies, for the work as it then stood was considerably larger than the present one.

As I went through it, I found so many unsatisfactory statements and uncertainties regarding the mode of action of drugs, which I thought I could decide by a few experiments, that I wished for a little time in order that those doubtful points might be settled; but as I went on the labour grew, other engagements became pressing, and longer and longer delay was required. From greater experience as a teacher and examiner also, I came to the conclusion that the plan of the work might be altered with advantage; and so finally the whole manuscript was thrown aside, and the book entirely re-written.

In the original work I discussed the physiological and therapeutical actions of each drug separately, in the same way as in the third part of the present work, though on a much more extended scale. I found, however, that this plan necessitated a good deal of repetition regarding the experimental methods by which the action of the drugs had been ascertained.

Moreover, the physician does not want to know only what the actions of any one drug are; he rather requires a knowledge of

classes of drugs, and of the manner in which the actions of the individual members of a class differ from each other. He requires, in fact, a knowledge of the ways in which the various functions of the body can be influenced by drugs both in health and disease, in order that he may restore health to his patients.

It has appeared to me, therefore, better to devote a complete section of the work to a discussion of the methods by which the action of drugs is determined; to the manner in which each function of the body can be modified by drugs; and to the general *rationale* of the use of drugs in disease, *i.e.* to devote a section to general pharmacology and general therapeutics.

Considerable experience both in teaching and examining has shown me that students sometimes find a difficulty in applying physiology to pharmacology and therapeutics, and I find that many others are, like myself, apt to forget those parts of physiology which they are not constantly studying. I have therefore thought it well, for the sake both of students and practitioners, to give a short account of the normal functions of the different parts of the body, before proceeding to discuss the alterations which are produced in them by drugs, or which they undergo in disease. In the case of the heart and the kidneys also, where the action of drugs is complicated and difficult, I have found it necessary to enter a little more fully into the physiology of these organs than is done in the ordinary text-books.

I have found that a similar difficulty occurs with pathology as with physiology, and I have therefore occasionally discussed pathological questions when I have thought that by doing so I could render the action of drugs in disease more intelligible, and thus aid the student of rational therapeutics.

In the second part of the work on general pharmacy, I have classed together the various pharmaceutical preparations, and given lists of them for reference. It is by no means my intention that these should be learned by heart by any student, and indeed I think it is well to take this opportunity of protesting against the injustice of the demands which are sometimes made upon the memories of students.

It is probable that the majority of the best and most successful practitioners would be very much puzzled if they were required to state the exact quantity of every ingredient in each pill or each ointment that they prescribe, or the exact quantity of the crude drug from which the infusions or tinctures which they use have been made. They know the action of the pill or ointment, they

know the action of the infusion or tincture, and they do not trouble themselves about details which are only useful to the chemist who is making up the preparation.

It is very greatly to be regretted, for it is a stumbling-block in the way of true progress, that students who have afterwards to become medical practitioners and not pharmaceutical chemists, should be asked at examinations the quantities of crude drugs from which particular preparations are made—quantities which even the manufacturing chemist himself would never dream of carrying in his memory, but would obtain by reference to his books whenever he required them. As the late Professor Sharpey used very truly to say, 'You may as well require of a medical student a knowledge of the whole art of cutlery before you set him to dissect.' Medical science is now advancing in every direction, and unless we cut off some of the less useful kinds of information, which medical students were formerly obliged to acquire, it becomes impossible for them to learn all that is truly valuable. In Materia Medica we now oblige them to learn the physiological action of drugs, a subject regarding which, until quite recently, little or nothing was known, and to oblige them to learn all this, in addition to what they were formerly expected to know, is to treat them as Pharaoh treated the Israelites, and compel them to make the same number of bricks, while giving them no straw.

I am so much impressed with the necessity of lessening the amount of unnecessary work sometimes required as a preparation for examinations, that at first I omitted from this book all reference to the composition of pharmaceutical preparations. But as it is intended not only as a text-book for students, but also for the use of practitioners, I afterwards considered that it might be convenient to have the composition of some pharmaceutical preparations, at least, for the purpose of reference. I have omitted the composition of such preparations as are like to be got ready-made from a chemist, but have inserted the composition of infusions which often need to be prepared when required. I have also given the composition of various compound pills, but only for the purpose of reference.

In consequence of this change in the plan of the work while it was passing through the press, the preparations of rhubarb have been omitted from their proper place at page 924, and are to be found at page 1005.

In the preparation of this work I have to acknowledge my

obligations to the admirable works of Bartholow, Binz, Buchheim, Dujardin-Beaumetz, Edes, Husemann, Nothnagel and Rossbach, Ringer, Schmiedeberg, and H. C. Wood. Messrs. Chapman, Soutter, Spencer, Spry,[1] Steinthal, Stubbs, Walsh,[1] Wells, and Wright for the excellent notes they took of my lectures; to Dr. D'Arcy Power for the verification of references; to Dr. Mitchell Bruce, Mr. T. W. Shore, and Mr. H. W. Gardner for much kind assistance in the preparation of the work, and to Prof. Matthew Hay, of Aberdeen, whose criticisms and suggestions have been invaluable. To Dr. Francis H. Williams, of Boston, Mass., I am indebted for the adaptation of this work to the United States Pharmacopœia, which by tending to familiarise medical men on each side of the Atlantic with the preparations employed in both countries may, I trust, tend to facilitate the introduction of an International Pharmacopœia.

T. LAUDER BRUNTON.

March, 1885.

[1] These names were inadvertently omitted in the preface to the first edition, but were mentioned in the preface to the second.

Articles and Preparations included in the British Pharmacopœia of 1885, which were not in that of 1867 nor in the 'Additions' of 1874.

Acidum Boricum.
Acidum Carbolicum Liquefactum.
Acidum Chromicum.
Acidum Hydrobromicum Dilutum.
Acidum Lacticum.
Acidum Lacticum Dilutum.
Acidum Meconicum.
Acidum Oleicum.
Acidum Phosphoricum Concentratum.
Acidum Salicylicum.
Alcohol Ethylicum.
Aloin.
Anisi Fructus.
Anisi Stellati Fructus.
Apomorphinæ Hydrochloras.
Aqua Anisi.
Argenti et Potassii Nitras.
Arsenii Iodidum.
Bismuthi Citras.
Bismuthi et Ammonii Citras.
Butyl-Chloral Hydras.
Caffeina.
Caffeinæ Citras.
Calamina Preparata.
Calcii Sulphas.
Calx Sulphurata.
Chrysarobinum.
Cimicifugæ Rhizoma.
Cinchonidinæ Sulphas.
Cinchoninæ Sulphas.
Coca.
Cocainæ Hydrochloras.
Codeina.
Collodium Vesicans.
Cupri Nitras.
Elaterinum.
Ergotinum.
Extractum Belladonnæ Alcoholicum.
Extractum Cascaræ Sagradæ.
Extractum Cascaræ Sagradæ Liquidum.
Extractum Cimicifugæ Liquidum.
Extractum Cocæ Liquidum.
Extractum Gelsemii Alcoholicum.
Extractum Jaborandi.
Extractum Rhamni Frangulæ.
Extractum Rhamni Frangulæ Liquidum.
Extractum Taraxaci Liquidum.
Gelsemium.
Glycerinum Aluminis.
Glycerinum Plumbi Subacetatis.
Glycerinum Tragacanthæ.
Infusum Jaborandi.
Injectio Apomorphinæ Hypodermica.
Injectio Ergotini Hypodermica.
Iodoformum.
Jaborandi.
Lamellæ Atropinæ.
Lamellæ Cocainæ.
Lamellæ Physostigminæ.
Liquor Acidi Chromici.
Liquor Ammonii Acetatis Fortior.
Liquor Ammonii Citratis Fortior.
Liquor Arsenii et Hydrargyri Iodidi.
Liquor Calcii Chloridi.
Liquor Ferri Acetatis.
Liquor Ferri Acetatis Fortior.
Liquor Ferri Dialysatus.
Liquor Morphinæ Bimeconatis.
Liquor Sodii Ethylatis.
Lupulinum.
Menthol.
Morphinæ Sulphas.
Oleatum Hydrargyri.
Oleatum Zinci.
Oleo-Resina Cubebæ.
Oleum Eucalypti.
Oleum Pini Sylvestris.
Oleum Santali.

Paraffinum Durum.
Paraffinum Molle.
Physostigmina.
Pilocarpinæ Hydrochloras.
Potassii Cyanidum.
Quininæ Hydrochloras.
Rhamni Frangulæ Cortex.
Rhamni Purshiani Cortex.
Salicinum.
Sodii Bromidum.
Sodii Iodidum.
Sodii Salicylas.
Sodii Sulphis.
Sodii Sulphocarbolas.
Sodium.
Spiritus Ætheris Compositus.
Spiritus Cinnamomi.
Staphisagriæ Semina.
Suppositoria Iodoformi.
Tabellæ Nitroglycerini.
Thymol.
Tinctura Chloroformi et Morphinæ.
Tinctura Cimicifugæ.
Tinctura Gelsemii.
Tinctura Jaborandi.
Tinctura Podophylli.
Trochisci Acidi Benzoici.
Trochisci Santonini.
Unguentum Acidi Borici.
Unguentum Acidi Carbolici.
Unguentum Acidi Salicylici.
Unguentum Calaminæ.
Unguentum Chrysarobini.
Unguentum Eucalypti.
Unguentum Hydrargyri Nitratis Dilutum.
Unguentum Iodoformi.
Unguentum Staphisagriæ.
Unguentum Zinci Oleati.
Vapor Olei Pini Sylvestris.
Zinci Sulphocarbolas.

Articles and Preparations included in the British Pharmacopœia of 1867 or in the 'Additions' of 1874, but omitted in the British Pharmacopœia of 1885.

Areca.
Cadmii Iodidum.
Castoreum.
Decoctum Ulmi.
Digitalinum.
Dulcamara.
Enema Tabaci.
Ferri Iodidum.
Ferri Oxidum Magneticum.
Ferri Peroxidum Humidum.
Hydrargyri Iodidum Viride.
Infusum Dulcamaræ.
Liquor Atropiæ.
Mistura Gentianæ.
Pilula Quiniæ.
Rhamni Succus.
Sodæ Acetas.
Stramonii Folia.
Syrupus Rhamni.
Tinctura Castorei.
Ulmi Cortex.
Unguentum Cadmii Iodidi.

Articles and Preparations the Names of which have been altered.

Former Names, 1867 or 1874.	Present Names, 1885.
Aconitia	Aconitina.
Albumen Ovi	Ovi Albumen.
Ammoniæ Benzoas	Ammonii Benzoas.
Ammoniæ Carbonas	Ammonii Carbonas.
Ammoniæ Nitras	Ammonii Nitras.
Ammoniæ Phosphas	Ammonii Phosphas.
Arnicæ Radix	Arnicæ Rhizoma.

Former Names, 1867 or 1874.	Present Names, 1885.
Assafœtida	Asafœtida.
Atropia	Atropina.
Atropiæ Sulphas	Atropinæ Sulphas.
Berberiæ Sulphas	Beberinæ Sulphas
Calcis Carbonas Præcipitata	Calcii Carbonas Precipitata.
Calcis Hydras	Calcii Hydras.
Calcis Hypophosphis	Calcii Hydrophosphis.
Calcis Phosphas	Calcii Phosphas.
Calx Chlorata	Calx Chlorinata.
Canellæ Albæ Cortex	Canellæ Cortex.
Cardamomum	Cardamomi Semina.
Cataplasma Sodæ Chloratæ	Cataplasma Sodæ Chlorinatæ.
Catechu Pallidum	Catechu.
Cinchonæ Flavæ Cortex	Cinchonæ Cortex.
Cinchonæ Pallidæ Cortex	Cinchonæ Cortex.
Decoctum Cinchonæ Flavæ	Decoctum Cinchonæ [Rubræ].
Ecbalii Fructus	Ecballii Fructus.
Emplastrum Cerati Saponis	Emplastrum Saponis Fuscum.
Enema Assafœtidæ	Enema Asafœtidæ.
Enema Magnesiæ Sulphatis	Enema Magnesii Sulphatis.
Extractum Cinchonæ Flavæ Liquidum	Extractum Cinchonæ [Rubræ] Liquidum.
Ferri et Ammoniæ Citras	Ferri et Ammonii Citras.
Ferri et Quiniæ Citras	Ferri et Quininæ Citras.
Hydrargyri Sulphas	Hydrargyri Persulphas.
Infusum Cinchonæ Flavæ	Infusum Cinchonæ [Rubræ] Acidum.
Liquor Ammoniæ Acetatis	Liquor Ammonii Acetatis.
Liquor Ammoniæ Citratis	Liquor Ammonii Citratis.
Liquor Atropiæ Sulphatis	Liquor Atropinæ Sulphatis.
Liquor Bismuthi et Ammoniæ Citratis	Liquor Bismuthi et Ammonii Citratis.
Liquor Calcis Chloratæ	Liquor Calcis Chlorinatæ.
Liquor Magnesiæ Carbonatis	Liquor Magnesii Carbonatis.
Liquor Magnesiæ Citratis	Liquor Magnesii Citratis.
Liquor Morphiæ Acetatis	Liquor Morphinæ Acetatis.
Liquor Morphiæ Hydrochloratis	Liquor Morphinæ Hydrochloratis.
Liquor Potassæ Permanganatis	Liquor Potassii Permanganatis.
Liquor Sodæ Arseniatis	Liquor Sodii Arseniatis.
Liquor Sodæ Chloratæ	Liquor Sodæ Chlorinatæ.
Liquor Strychniæ	Liquor Strychninæ Hydrochloratis.
Lithiæ Carbonas	Lithii Carbonas.
Lithiæ Citras	Lithii Citras.
Magnesia	Magnesia Ponderosa.
Magnesiæ Carbonas	Magnesii Carbonas Ponderosa.
Magnesiæ Carbonas Levis	Magnesii Carbonas Levis.
Magnesiæ Sulphas	Magnesii Sulphas.
Morphiæ Acetas	Morphinæ Acetas.
Morphiæ Hydrochloras	Morphinæ Hydrochloras.
Physostigmatis Faba	Phosostigmatis Semen.
Pilula Aloes et Assafœtidæ	Pilula Aloes et Asafœtidæ.
Pilula Assafœtidæ Composita	Pilula Asafœtidæ Composita.
Podophylli Radix	Podophylli Rhizoma.
Potassæ Acetas	Potassii Acetas.
Potassæ Bicarbonas	Potassii Bicarbonas.
Potassæ Bichromas	Potassii Bichromas.

Former Names, 1867 or 1874.	Present Names, 1885.
Potassæ Carbonas	Potassii Carbonas.
Potassæ Chloras	Potassii Chloras.
Potassæ Citras	Potassii Citras.
Potassæ Nitras	Potassii Nitras.
Potassæ Permanganas	Potassii Permanganas.
Potassæ Prussias Flava	Potassii Ferrocyanidum.
Potassæ Sulphas	Potassii Sulphas.
Potassæ Tartras	Potassii Tartras.
Potassæ Tartras Acida	Potassii Tartras Acida.
Quiniæ Sulphas	Quininæ Sulphas.
Serpentariæ Radix	Serpentariæ Rhizoma.
Sodæ Arsenias	Sodii Arsenias.
Sodæ Bicarbonas	Sodii Bicarbonas.
Sodæ Carbonas	Sodii Carbonas.
Sodæ Carbonas Exsiccata	Sodii Carbonas Exsiccata.
Sodæ Citro-tartras Effervescens	Sodii Citro-tartras Effervescens.
Sodæ Hypophosphis	Sodii Hypophosphis.
Sodæ Nitras	Sodii Nitras.
Sodæ Phosphas	Sodii Phosphas.
Sodæ Sulphas	Sodii Sulphas.
Sodæ Valerianas	Sodii Valerianas.
Strychnia	Strychnina.
Suppositoria Morphiæ	Suppositoria Morphinæ.
Suppositoria Morphiæ cum Sapone	Suppositoria Morphinæ cum Sapone.
Tinctura Assafœtidæ	Tinctura Asafœtidæ.
Tinctura Quiniæ	Tinctura Quininæ.
Tinctura Quiniæ Ammoniata	Tinctura Quininæ Ammoniata.
Trochisci Morphiæ	Trochisci Morphinæ.
Trochisci Morphiæ et Ipecacuanhæ	Trochisci Morphinæ et Ipecacuanhæ.
Trochisci Potassæ Chloratis	Trochisci Potassii Chloratis.
Trochisci Sodæ Bicarbonatis	Trochisci Sodii Bicarbonatis.
Unguentum Aconitiæ	Unguentum Aconitinæ.
Unguentum Atropiæ	Unguentum Atropinæ.
Unguentum Veratriæ	Unguentum Veratrinæ.
Valerianæ Radix	Valerianæ Rhizoma.
Vapor Coniæ	Vapor Coninæ.
Veratria	Veratrina.
Veratri Viridis Radix	Veratri Viridis Rhizoma.
Vinum Quiniæ	Vinum Quininæ.

Substitutions.

Antimonium Nigrum Purificatum	*for*	Antimonium Nigrum.
Cinchonæ Rubræ Cortex (in preparations)	"	Cinchonæ Flavæ Cortex. Cinchonæ Pallidæ Cortex.
Pulvis Elaterini Compositus	"	Pulvis Elaterii Compositus.
Tinctura Cinchonæ [Rubræ]	"	Tinctura Cinchonæ Flavæ.
Unguentum Glycerini Plumbi Subacetatis	"	Unguentum Plumbi Subacetatis Compositum.

Preparations the Composition of which has been altered.

(Minor alterations are not included.)

Acidum Sulphurosum.
Alumen.
Antimonium Sulphuratum.
Extractum Cinchonæ Liquidum.
Infusum Cinchonæ Acidum.
Injectio Morphinæ Hypodermica.
Liquor Epispasticus.
Liquor Iodi.
Oleum Phosphoratum.
Pilula Phosphori.
Pulvis Glycyrrhizæ Compositus.
Tinctura Quininæ.
Unguentum Hydrargyri Ammoniati.
The fatty basis of the four suppositories of B.P. 1867 is now oil of theobroma only.
In some of the ointments paraffins have been substituted for lard.
Scammony Resin has been substituted for Scammony in most preparations of Scammony.

The strengths of the following preparations have been altered from 1 *in* 109 *to* 1 *in* 100.

Liquor Arsenicalis.
Liquor Arsenici Hydrochloricus.
Liquor Atropinæ Sulphatis.
Liquor Morphinæ Acetatis.
Liquor Morphinæ Hydrochloratis.
Liquor Potassii Permanganatis.
Liquor Sodii Arseniatis.
Liquor Strychninæ Hydrochloratis.

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MATERIA MEDICA AND THERAPEUTICS.

B

INTRODUCTION.

By **Materia Medica** we understand a knowledge of the remedies employed in medicine. This knowledge may be subdivided into several divisions: Materia Medica proper, Pharmacy, Pharmacology, and Therapeutics.

By **Materia Medica proper** we mean an acquaintance with the remedies used in medicine, the places whence they come, the crude substances, plants or animals which yield them, the methods by which they are obtained, and the means of distinguishing their goodness or purity, or of detecting fraudulent adulteration.

By **Pharmacy** we mean the methods by which drugs are prepared and combined for administration.

By **Pharmacology** we mean a knowledge of the mode of action of drugs upon the body generally, and upon its various parts. It is of comparatively recent growth, but is now one of the most important subdivisions of Materia Medica.

By **Therapeutics** we understand a knowledge of the uses of medicines in disease.

Therapeutics may be either *empirical* or *rational*. By **empirical** we mean that drugs are tried haphazard, or with little knowledge of their action in some cases, and, being found successful, are again administered in other cases which seem to be similar.

Perhaps the best example of the empirical use of a remedy is that of quinine in ague. We do not know with certainty what the pathological conditions are in this disease, nor how quinine acts upon them; all we know is that it has proved useful in cases of ague before, and therefore we give it again.

Rational therapeutics consists in the administration of a drug because we know the pathological conditions occurring in the disease, and know also that the pharmacological action of the drug is such as to render it probable that it will remove or counteract these conditions.

Rational therapeutics is the highest branch of medicine. Its advance is necessarily slow, because it is based upon pathology on the one hand and pharmacology on the other, and both of these rest upon physiology, which in its turn rests upon physics and chemistry. It is only with the development of the

fundamental sciences that those which rest upon them can grow; and when we consider that chemistry as a science is not much more than a hundred years old, and when we see the advances it has already made, we cannot but be hopeful for the future of therapeutics.

Occasionally we hear the question asked, 'What is the use of knowing the action of all sorts of drugs upon the different parts of the animal body, and what is the use of knowing the alterations in the muscles, vessels, or nerves which occur under pathological conditions, seeing that in many instances such a knowledge cannot be utilised for the treatment of disease?' As well might we ask, on seeing a half-built bridge, 'What is the use of laying the foundations and building the piers, seeing no one can walk across from one end to the other?'

As an example of rational therapeutics, we may take the use of nitrite of amyl in certain forms of angina pectoris. The obvious symptoms in this disease are intense pain in the region of the heart, and fear of impending death. Sphygmographic tracings of the pulse taken during this condition show that the tension within the heart and vessels begins to increase as the pain comes on, and reaches such a height that the heart can barely empty itself. Observations on animals have shown that nitrite of amyl lessens the tension of the blood in the vessels; and we therefore give it in angina pectoris with the expectation that it will diminish the tension and remove the pain, and we find that it succeeds.

But this example shows us only the first stage of rational therapeutics. We have removed by a remedy the pathological condition which immediately gives rise to the pain and danger of the patient, but the antecedent alterations of the heart, bloodvessels, and nervous system, which led to the occurrence of the pain, are unaltered by the remedy. In order that our therapeutics should be completely successful, we must seek still further for something which will restore the circulation and nervous system to its normal condition and bring the patient back to a state of perfect health.

Sometimes we are able to do this. For example, we occasionally meet with a kind of pain in the cardiac region which closely resembles angina pectoris, and is probably a form of it. Acting on the general principle that pain is due to irritation somewhere, though not necessarily at the place where the pain is felt, we seek for the irritant. We find swelling and tenderness over the sternum at the junction of the manubrium and the body, and we look upon this as the irritant which is exciting the cardiac pains. Judging this swelling to be syphilitic, we give iodide of potassium; the swelling subsides, and the angina-like pain completely disappears.

But sometimes it is impossible to remove the cause of the

disease, and all that we can do is to alleviate symptoms. The organic changes which have occurred in the course of the disease may be so great that we can hardly hope that any remedy will ever be discovered sufficiently powerful to remove them. We must therefore try to prevent them.

Preventive medicine, or **prophylaxis**, is daily becoming more important, and, possibly before the end of this century, medical men will be employed more to prevent people from becoming ill than to cure them when disease has become fairly established.

This may at least be the case in regard to the contagious and infectious diseases, which attack people as it were by accident, and are totally unconnected with their ordinary work or pleasure. It is too much to hope that other diseases which depend upon hereditary tendencies, overwork, or over-indulgence, will disappear, for there can be little doubt that men in the future will, as in the past, knowingly sacrifice, not only their health, but their life, to ambition, duty, or pleasure.

The advance of this branch of medicine has been greatly aided by the recent increase in our knowledge of the life-history of microbes and their action in causing disease. Our power to prevent disease will become greater when we know accurately the action of various drugs in destroying these microbes or preventing their growth.

Pharmacology has made such rapid advances of late years that it is exceedingly difficult for many men who are engaged in practice to understand thoroughly either the methods by which it is studied, or its results. Many students also, although they may be able to pass a good examination in physiology, find it difficult to apply their physiological knowledge to pharmacology; and therefore in discussing the action of drugs upon the various functions of the body, I have sometimes entered more fully into the physiology of those functions than may seem to some at all either necessary or advisable.

In discussing pharmacological questions, we are accustomed to speak of the **action** of a drug on the body or on its various parts; but we must remember the effect produced is not due to a one-sided action—that what we actually mean is the **re-action** between the drug and the various parts of the body.

In some instances we know that the drug itself is changed in the body, as well as the function of the body modified by the drug; and even in those cases where the drug itself is eliminated from the body apparently unaltered, it is probable that it has entered into various chemical combinations within the body while circulating in the blood or present in the tissues.

SECTION I.

GENERAL PHARMACOLOGY AND THERAPEUTICS.

CHAPTER I.

GENERAL RELATIONS BETWEEN THE ORGANISM AND SUBSTANCES AFFECTING IT.

In discussing the inter-action between the animal organism and the substances which act upon it, it may be well to take a slight glance first at the substances which compose its environment, although these will be afterwards considered more in detail.

Of the **elements** composing the earth on which we live we at present know about seventy-two whose existence appears well-established. They are given in the accompanying table. The atomic weights assigned to them cannot be regarded as absolutely correct. There are sometimes considerable discrepancies between those given by different authorities, and those which are accepted to-day may require to be altered again in accordance with the more exact knowledge which future observations may supply. There are slight differences between several of them as given in the British and United States Pharmacopœias.

TABLE OF ELEMENTS.

Element	Symbol	Valency or Atomicity	Atomic Weight, B.P.	Atomic Weight, U.S. P.	Atomic Weight very accurately determined[1]
*Aluminium	Al	II. & IV.	27·0	27·0	27·009
*Antimony (Stibium)	Sb	III. & V.	120·0	120·0	119·555
**Arsenicum*	*As*	III. & V.	75·0	74·9	74·918
*Barium	Ba	II.	137·0	136·8	136·763
Beryllium or Glucinum	Be or G	II.	9·0	9·0	9·085
*Bismuth	Bi	III. & V.	209·0	210·0	207·523
**Boron*	*B*	—	11·0	11·0	10·941
**Bromine*	*Br*	I.	80·0	79·8	79·768
Cadmium	Cd	II.	111·8	111·8	111·835
Cæsium	Cs	I.	133·0	132·6	132·583
*Calcium	Ca	II.	40·0	40·0	39·99
**Carbon*	*C*	II. & IV.	12·0	12·0	11·9736
*Cerium	Ce	IV.	141·0	141·0	140·424
**Chlorine*	*Cl*	I.	35·5	35·4	35·37
*Chromium	Cr	II. & IV.	52·5	52·4	52·009
Cobalt	Co	II. & IV.	58·9	58·9	58·887

Those marked with * are contained, either simply or in combination, in the British Pharmacopœia. Those printed in italics are non-metallic elements. Their atomic weights are given as in the B. P.

[1] From Ira Remsen's *Principles of Theoretical Chemistry*.

TABLE OF ELEMENTS—*continued.*

Element	Symbol	Valency or Atomicity	Atomic Weight, B.P.	Atomic Weight, U.S. P.	Atomic Weight very accurately determined
Columbium *vide* Niobium					
*Copper (Cuprum)	Cu.	II.	63·4	63·2	63·173
Didymium	Di.	IV.	145·4	144·6	145·4
Erbium	Er or Eb[1] or E	—	166·0	165·9	165·891
Fluorine	*F*	I.	19·0	19·0	18·984
Gallium	Ga	IV.	70·0	68·8	69·9
*Gold (Aurum)	Au	I. & III.	196·5	196·2	196·155
Glucinum *vide* Beryllium					
Holmium	. .	—	—	—	—
**Hydrogen*	*H*	I.	1·0	1·0	1·0
Indium	In	I. & III.	113·4	113·4	113·398
**Iodine*	*I*	I.	127·0	126·6	126·557
Iridium	Ir	II. & IV.	192·7	192·7	192·651
*Iron (Ferrum)	Fe	II. & IV.	56·0	55·9	55·913
Lanthanum	La	IV.	139·0	138·5	138·526
*Lead (Plumbum)	Pb	II. & IV.	207·0	206·5	206·471
*Lithium	Li	I.	7·0	7·0	7·0073
*Magnesium	Mg	II.	24·0	24·0	23·959
*Manganese	Mn	II. & IV.	55·0	54·0	53·906
*Mercury (Hydrargyrum)	Hg	II.	200·0	199·7	199·712
Molybdenum	Mo		95·5	95·5	95·527
Nickel	Ni	II. & IV.	58·0	58·0	57·928
Niobium or Columbium	Nb	V.	94·0	94·0	—
**Nitrogen*	*N*	III. & V.	14·0	14·0	14·021
Osmium	Os	II. & IV.	198·5	198·5	198·494
**Oxygen*	*O*	II.	16·0	16·0	15·9633
Palladium	Pd	II. & IV.	105·7	105·7	105·737
**Phosphorus*	*P*	III. & V.	31·0	31·0	30·958
*Platinum	Pt	II. & IV.	195·0	194·4	194·415
*Potassium (Kalium)	K	I.	39·0	39·0	39·019
Rhodium	Rh	II. & IV.	104·0	104·1	104·055
Rubidium	Rb	I.	85·3	85·3	85·251
Ruthenium	Ru	II. & IV.	104·2	104·2	104·217
Samarium	Sm	—	150·0	—	150·021
Scandium	Sc	—	44·0	44·0	43·98
Selenium	*Se*	II.	78·8	78·8	78·797
Silicon	*Si*	IV.	28·0	28·0	28·195
*Silver (Argentum)	Ag	I. (? II.)	108·0	107·7	107·7
*Sodium (Natrium)	Na	I.	23·0	23·0	22·998
Strontium	Sr	II.	87·4	87·4	87·374
**Sulphur*	*S*	II.	32·0	32·0	31·984
Tantalum	Ta	III. & V.	182·0	182·0	182·144
Tellurium	*Te*	II.	128·0	128·0	127·96
Terbium	. .	—	—	—	—
Thallium	Tl or Th	III.	203·7	203·7	203·715
Thorium	Th	IV.	233·0	233·0	233·414
Thulium	. .	—	—	—	—

[1] Er, Roscoe and Schorlemmer, *Treatise on Chemistry*, vol. i. p. 54. Eb, Fownes, edited by Watts, 12th ed. vol. i. p. 401. E, Ira Remsen's *Principles of Theoretical Chemistry*.

TABLE OF ELEMENTS—*continued.*

Element	Symbol	Valency or Atomicity	Atomic Weight, B.P.	Atomic Weight, U.S. P.	Atomic Weight very accurately determined
*Tin (Stannum) .	Sn. .	II. & IV.	118·0	117·7	117·698
Titanium . .	Ti . .	IV.	49·8	48·0	49·846
Tungsten . .	W . .	VI.	184·0	183·6	183·61
Uranium . .	U . .	IV. & VI.	240·0	238·5	239·8
Vanadium . .	V . .	III. & V.	51·3	51·3	51·256
Ytterbium . .	Yb. .	—	172·8	172·7	172·761
Yttrium . .	Y . .	IV.	89·8	89·8	89·816
*Zinc . .	Zn .	II.	65·0	64·9	64·9045
Zirconium . .	Zr. .	IV.	90·0	90·0	89·367

Nature of the Elements.

Considerable additions have been made to the number of elements during late years. The reason of this is that the spectroscope has indicated the presence of metals previously unknown, and by the use of proper means they have been obtained in a separate condition. These substances are termed elements because we do not at present know how to split them up in such a manner as to prove that they are compounds. But it is not improbable that they are compounds, just as we now know that potash and soda are compounds; although before Sir Humphry Davy split them up into oxygen and a metal they were supposed to be elements. Indeed, recently much evidence has been brought to show that the substances which we call elements are really compounds.

It is from an examination of the spectroscopic character of the elements at different degrees of temperature that Lockyer has been able to obtain sufficient data to justify the definite formulation of the **hypothesis** that all the **elements** we know are really compounds, or, to speak perhaps more precisely, are really **different forms** of aggregation of one kind **of matter.**[1] According to this hypothesis the matter of which the universe is composed was at one time equally distributed through space, and uniform in kind. The atoms then coalesced in various groups of two, three, or more; and these, again grouping themselves together still further, formed aggregates of more and more complex composition. These aggregates are, it is supposed, the elements with which we are acquainted. Most of those complex molecules are perfectly stable at ordinary temperatures; and so their composition remains constant under the conditions usual at the surface of this earth.

But when they are subjected to increased temperatures in the laboratory, rising from that of the Bunsen lamp to the electric arc, and then to the electric spark or to still higher temperatures in the sun, their spectroscopic appearances give evidence of decomposition into simpler molecules. When the elements are subjected to cold and pressure the molecules which compose them come closer together, and we get them forming a solid substance. Heat tends, by communicating vibrations to them, to shake the molecules further apart, and to produce a liquid condition. Still greater heat shakes the molecules further apart still, and produces a gaseous condition.

In all those conditions the molecules of the element become more complex by reduction of temperature or increase of pressure, and simpler by increase in temperature or reduction in pressure.[2] Exceedingly great heat or electricity appears to shake apart still further the constituents of the element, so as to resolve it into simpler combinations of the elementary substance of which, according to the hypothesis, it is composed.

This shaking apart of the component elements is known to exist in com-

[1] Lockyer, *Phil. Trans.* 1874, p. 492 *et seq.*

[2] According to another hypothesis, bodies are supposed to have molecules of one degree of complexity, and the difference between solid, liquid, and gaseous bodies is

pounds, and to it the name of **dissociation** has been given. Thus when chalk or limestone is exposed to the action of heat it becomes dissociated into carbonic acid and lime, $CaCO_3 = CaO + CO_2$. This process is readily reversible by reversing the conditions. Thus the lime and carbonic acid which are dissociated by heat readily recombine in the cold $CaO + CO_2 = CaCO_3$.

When matter is **solid** the molecules of which it is composed are supposed to be large and close together. When in the state of vapour or **gas**, these molecules are smaller and much further apart.

Solid, liquid, or densely gaseous matter, when its molecules are agitated by heat, gives a continuous spectrum. Gaseous and vaporous matters, when their molecules are agitated at lower pressures or higher temperatures by heat or electricity, give a discontinuous spectrum consisting of bands or lines.

Between those extremes we have, as a rule, three other intermediate kinds of spectra: first, a continuous spectrum in the red; next, a continuous spectrum in the blue; next, a fluted spectrum, and after that the line spectrum already mentioned.

In all those kinds of spectrum, however, we are supposing that the elementary molecules are still intact; they are only more or less separated.

Compound bodies, like simple bodies, give definite spectra. The spectrum of a simple metal consists of lines which increase in number and thickness as the pressure of the vapour or its quantity in a given space is increased. The spectrum of a compound body consists chiefly of channelled spaces and bands which increase in the same manner. The greater the number of molecules in a cubic inch or cubic millimetre, and the more violently they are agitated, the more complex is the spectrum until it becomes continuous.

The smaller the number of molecules in a given space, the more simple is the spectrum, which then consists of a few lines only.

When a compound is exposed to heat, so as to dissociate it into its component parts the spectroscopic bands characteristic of the compound become thinner, and the lines of the metal increase in number, as shown in the accompanying diagram where the bands exhibited by calcium chloride in the flame of a Bunsen's burner, disappear, and are replaced by lines only, when

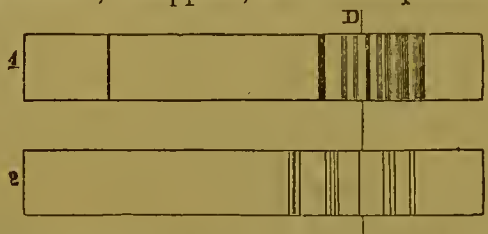

FIG. 1.—Spectrum of calcium chloride. (1) In the flame of a Bunsen's burner, showing the channelled spaces and bands of a compound. (2) In an electric spark, showing the lines of the element calcium. (After Roscoe.)

an electric spark is used. When an element is treated with more and more heat and electricity it likewise gives exactly the same kind of evidence of dissociation—bands disappearing, and lines becoming thinner. Besides this, new lines make their appearance with every large increase of temperature.

This behaviour of the element appears to show that it also is a compound, but that it is stable under ordinary conditions, and is only dissociated at a high temperature.

Other proofs of this hypothesis are derived from a comparison of the spectra of the elements as observed in our laboratories with their spectra in the sun.

A comparison of the two hypotheses shows us that as on the old hypothesis each element represents a species and is unvariable, its spectrum ought to be always the same in our laboratories and in the sun: and the same in sun-spots as in prominences, and the same at all periods of the sun's activity.

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supposed to depend on the difference in the free path of the molecule. But according to the new view, the difference in the complexity of the molecule itself is sufficient to explain the phenomena.

Under the new hypothesis the spectra of metals in our laboratories and in the sun should not resemble each other; they should be different in sun-spots and in prominences, because the spot is cooler than the prominence; and they should vary at the time of the sun's activity because the sun is hotter at the maximum of the sun-spot period, and therefore there should be a greater amount of dissociation amongst the elements at that period.

As a matter of fact we find that the spectra in our laboratories and in the sun do not resemble each other (Fig. 2); that those of the same element

FIG. 2.—Diagram of the spectrum of lithium under various conditions of temperature. (After Lockyer, *Roy. Soc. Proc.* Dec. 12, 1878.)

in the sun-spot and prominences are as dissimilar as of any two elements; and that the spectra of the elements in the sun do vary with the maximum of the sun-spot period.

On the old hypothesis the spectra of prominences should also consist of lines familiar to us in our laboratories, because solar and terrestrial elements are the same, while, according to the new hypothesis, the spectra of prominences should be unfamiliar, because the prominences represent outpourings from a body hot enough to prevent the atoms of which our elements are composed from coming together.

As a matter of fact, the lines in the prominences, with the exception of those of hydrogen, magnesium, calcium, and sodium, are either of unknown origin, or are feeble lines in the spectra of known elements. **Spectroscopic observation**, therefore, leads to the belief that the so-called **elements are really compounds,** the component parts of which are kept apart by high temperatures in the sun and stars, but unite when the temperature decreases.

By the powerful vibrations imparted to them by the electric spark, they may be dissociated in the laboratory; but, as no means has yet been devised of separating the components, they again unite to form the original body, just as hydrogen and oxygen, into which steam is dissociated by passing it through a strongly heated tube, almost instantly combine again to form water unless they are separated by means of the more rapid diffusion of hydrogen through a porous tube.

The difficulty in accepting this evidence lies in the fact that we have hitherto been unable to isolate the substances into which the elements are supposed to be dissociated; as these after their dissociation at once recombine and again form the original substance.

One proof, however, that the supposed components of the element calcium may remain permanently separated, is afforded by the fact that in the spectra of two stars, Sirius (Fig. 3) and α Lyræ, which are very bright, and probably very hot, only one of the ultra-violet lines of calcium is represented.

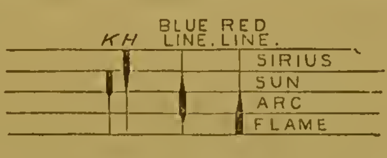

FIG. 3.—Diagram of the spectrum of calcium under various conditions of temperature. In the spectrum of Sirius the line K is absent, while it is very strongly marked in the solar spectrum.

But we have also other evidence of the compound nature of the elements, which, although it was not sufficient of itself to force us to abandon our old ideas of their simple nature, is yet strongly corroborative of the spectroscopic evidence. Thus we find that **oxygen** is broken up by electricity, and that the atoms of which its molecules are composed, rearrange themselves so as to form what is to all intents and purposes a new element, ozone, having a much closer resemblance to chlorine than to oxygen in its activity,

although its compounds with metals appear to be identical with those of oxygen.

a b

FIG. 4.—Diagram to illustrate the formation of ozone by electricity. *a* represents oxygen, through which a spark is passing; *b* after it has passed. The double rings are intended to represent molecules of oxygen, each containing two atoms. As the electric spark passes through the oxygen it breaks up the first molecule, carrying one atom on to join the second molecule of oxygen, and form one of ozone. The atom which is left joins another molecule of oxygen, and also forms ozone. (After Lockyer.)

At a high temperature its atoms are again dissociated, and recombine to form ordinary oxygen. When it combines with other substances, the heat of combination appears to be sufficient to dissociate the atoms of ozone (O_3), so that in the compound we meet with simple oxygen, O.

When **sulphur** is simply melted and cooled, it solidifies as a yellow brittle substance, but if it is heated to 200° it becomes brownish and thick, and if it be suddenly cooled, by throwing it into water, it solidifies as a transparent reddish plastic and elastic substance. The ordinary brittle and yellow, and the reddish plastic sulphur, appear to be quite different substances. But if the plastic sulphur be left for some hours, it becomes reconverted into ordinary sulphur; and if either ordinary or plastic sulphur be volatilised, the vapour condenses in the form of ordinary sulphur; but if the vapour is quickly cooled, the sulphur, while retaining its ordinary appearance, may yet undergo a certain change evidenced by its becoming insoluble in bisulphide of carbon. On the new hypothesis we explain these phenomena by supposing that the different forms of sulphur are different compounds, or perhaps we should rather say different aggregates, for their components may not differ in kind like those of calcium, but only in number like those of oxygen or ozone.

Indeed we are almost driven to such a conclusion by the behaviour of sulphur in regard to its vapour density, for only at very high temperatures does the specific gravity of the vapour follow the general rule, and at lower temperatures it is three times as great as it ought to be, indicating that at these lower temperatures the molecule of sulphur contains six atoms instead of two.

Phosphorus also affords us an example of an element which occurs in two forms, so different that we should call them distinct bodies, were it not that we find that one can be transformed into the other.

The two forms, red and yellow phosphorus, differ from each other, not only in their colour, but in their density, specific heat, readiness of combustion, and heat of combustion. They differ also in the fact that yellow phosphorus is exceedingly poisonous, whereas the red phosphorus is not poisonous. They are in many respects, then, different bodies, but we have hitherto been content to call them allotropic forms of the same element.

In combination we find that phosphorus is sometimes *pentad* and sometimes *triad*; that its compounds with oxygen are sometimes poisonous, at other times not. Thus orthophosphoric acid, H_3PO_4, is not poisonous; pyrophosphoric acid, $H_4P_2O_7$, and metaphosphoric acid, HPO_3, are both poisonous.

The most striking example, however, is **carbon**, which we not only find

in three forms, differing enormously from each other, as diamond, charcoal, and graphite, but which we find in various compounds playing the most varied parts. This we at present explain by saying that carbon unites with itself in the formation of the various radicals ; and thus comes to form what are practically new elements.

Another example is afforded us by **ammonia**, the salts of which are just as well characterised as those of potash or soda. The amalgam which it forms with mercury possibly indicates that we have in it also a real metal, ammonium, corresponding to sodium or potassium, though this is uncertain.

The three metals, sodium, potassium, and ammonium (if it exist), agree in the readiness with which they are oxidised, so that it is difficult to preserve the pure metal, although the oxide is stable. They differ, however, in the oxides of potassium and sodium being solid, and that of ammonium gaseous. Ammonium has not been isolated, and it is put down in the text-books as a hypothetical substance, but ammonium salts are tangible enough, and the question which we have to keep before us is, whether potassium, sodium, and all the other so-called elements, are not in reality compounds like ammonium.

Some people still regard species as immutable, and look upon Darwin's hypothesis of evolution as unproven.

The evidence in favour of the evolution of elements from one simple form of matter, is as yet, perhaps, much less strong than that in support of the evolution of species ; but the hypothesis has this advantage, that it explains certain phenomena which have hitherto been very perplexing.

It may be at least convenient in discussing the physiological action of drugs to bear this hypothesis in mind, and to remember that what we have hitherto been accustomed to call elements may be really constituted like the so-called organic radicals, with this difference, that we can split up organic radicals with tolerable facility, while we cannot do this—at least to any great extent—with elements.

It also shows us that we must as pharmacologists pay attention to **molecular** as well as to **empirical composition**, and take into consideration crystalline form and physical aggregation in all observations regarding the relations between elements or compounds and living organisms. It is not sufficient, for example, to speak of the action of phosphorus on the organism as if this were invariable, for it varies with the molecular composition of the body in the red or yellow form, and isomeric organic substances may be utterly different in action.

Classification of the Elements.

The vegetable and animal kingdoms are divided into various groups. Formerly, men tried to arrange them in linear succession so that there should be an unbroken line from the lowest to the highest members of the vegetable kingdom, thence to the lowest member of the animal, and onwards up to the highest member of the animal kingdom. Such an arrangement as this, however, was found to be unnatural. Instead of the highest members of the vegetable kingdom being connected with the lowest members of the animal kingdom, it is found that the lowest members of each kingdom are closely connected and that the divergence becomes greater as development proceeds towards the highest members in each kingdom. The doctrine of **evolution** at once rendered this arrangement natural and easily understood.

Starting from one common point of origin in structureless protoplasm, the various organisms became more and more unlike in each successive stage of development, their resemblance being only recognisable at all in their embryonic condition.

Various attempts have been made to arrange inorganic substances in natural orders. One mode of **arrangement** is according to their **atomic weight**—as in the following table :—[1]

[1] In this and the following Tables the atomic weights have been corrected.

Element	Atomic Weight	Difference	Element	Atomic Weight	Difference	Element	Atomic Weight	Difference	Element	Atomic Weight	Difference
H	1		K	39	3·5	Y	89·8	2·4	Ce	141	2
Li	7	6	Ca	40	1	Zr	90	0·2	Di	145·4	3·6
G or Be	9	2	Ti	49·8	9·8	Nb	94	4	Ta	182	36·6
			V	51·3	1·5	Mo	95·5	1·5	W	184	2
B	11	2	Cr	52·5	1·2	Rh	104	8·5	Ir	192·7	8·7
C	12	1	Mn	55	2·5	Ru	104·2	0·2	Pt	195	2·3
N	14	2	Fe	56	1	Pd	105·7	1·5	Au	196·5	1·5
O	16	2	Ni	58	2	Ag	108	2·3	Os	198·5	2
Fl	19	3	Co	58·9	0·9	Cd	111·8	3·8	Hg	200	1·5
Na	23	4	Cu	63·4	4·5	Sn	118	6·2	Tl	203·7	3·7
Mg	24	1	Zn	65	1·6	Sb	120	2	Pb	207	4
Al	27	3	As	75	10	I	127	7	Bi	209	3
Si	28	1	Se	78·8	3·8	Te	128	1	Th	233	24
P	31	3	Br	80	1·2	Cs	133	5	U	240	7
S	32	1	Rb	85·3	5·3	Ba	137	4			
Cl	35·5	3·5	Sr	87·4	2·1	La	139	2			

From this it will be seen that the atomic weights of the different elements form a series, the members of which in most cases differ from one another by 1, 2, 3, or 4. There are few exceptions in which the differences are much greater, and these probably represent blanks which may yet be filled up as our knowledge of the elements increases. This mode of classification, however, reminds us of the Linnæan system in plants, and is artificial rather than natural. In it, the elements which are placed close together possess very different properties, whereas those which are separated from each other present considerable resemblances.

NEWLAND'S TABLE.

Member of a Group having Lowest Equivalent		One immediately above the preceding		Difference	
				H = I	O = I
Magnesium	24	Calcium	40	16	1
Oxygen	16	Sulphur	32	16	1
Lithium	7	Sodium	23	16	1
Carbon	12	Silicon	28	16	1
Fluorine	19	Chlorine	35·5	16·5	1·031
Nitrogen	14	Phosphorus	31	17	1·062
Lowest term of Triad		**Highest term of Triad**			
Lithium	7	Potassium	39	32	2
Magnesium	24	Cadmium	112	88	5·5
Molybdenum	96	Tungsten	184	88	5·5
Phosphorus	31	Antimony	120	89	5·687
Chlorine	35·5	Iodine	127	91·5	5·718
Potassium	39	Cæsium	141	102	5·875
Sulphur	32	Tellurium	128	96	6·062
Calcium	40	Barium	137	97	6·062

The first important attempt at a **natural classification** of the elements was made by Newlands in 1864.[1] He then arranged them in **groups**, between the members of which there was a close connection in regard to their chemical properties, and a curious relation in regard to their atomic weights. These presented differences which were generally multiples of the atomic weight of hydrogen, and generally equal to, or multiples of, that of oxygen.

A curious relationship had also been pointed out by M. Dumas[2] between the members of the potassium group, their atomic weights being equal to multiples of those of lithium and potassium added together.

Li + K = 2Na,	or in figures,	7 + 39 = 46
Li + 2K = Rb	,,	7 + 78 = 85
2Li + 3K = Cs (133)[3]	,,	14 + 117 = 131
Li + 5K = Tl (203·7)	,,	7 + 195 = 202
3Li + 5K = 2Ag	,,	21 + 195 = 216

A similar relation was also pointed out by Mr. Newlands between lithium and the calcium group; as follows:—

Li + Ca = 2Mg (48),	or in figures,	7 + 40 = 47
Li + 2Ca = Sr	,,	7 + 80 = 87
2Li + 3Ca = Ba (137)	,,	14 + 120 = 134
Li + 5Ca = Pb	,,	7 + 200 = 207

But Mr. Newland's most important table is the following one, in which he has arranged the elements in ten **series**:—

			Triad			
			Lowest term	Mean	Highest term	
I.		Li 7	+17 = Mg 24	Zn 65	Cd 111·8	
II.		B 11				Au 196
III.		C 12	+16 = Si 28		Sn 118	
IV.		N 14	+17 = P 31	As 75	Sb 120	+88 = Bi 210
V.		O 16	+16 = S 32	Se 78·8	Te 128	+70 = Os 199
VI.		F 19	+16·5 = Cl 35·5	Br 80	I 127	
VII.	Li 7	+16 = Na 23	+16 = K 39	Rb 85·3	Cs 133	+70 = Tl′ 203
VIII.	Li 7	+17 = Mg 24	+16 = Ca 40	Sr 87·4	Ba 137	+70 = Pb 207
IX.			V 51·3		W 184	
X.			Mo 95·5		Pt 195	
			Pd 105·7			

Seven of these series nearly correspond in their first members with those of Mendelejeff, to whom and to Lothar Meyer we owe the complete development of this mode of classification. Mr. Newlands also pointed out that the eighth element starting from a given one, was a kind of repetition of the first, like the eighth note of an octave in music.[4]

Mendelejeff has not only greatly developed this system of classification, but has afforded convincing proof of its value by not only predicting the existence of an unknown element, but actually describing its physical characters and chemical reactions—a prediction the correctness of which was proved by the discovery of gallium, and by the agreement of its characters and reactions with those which Mendelejeff had foretold.

The various members of the animal kingdom can all be arranged in a few series: Protozoa, Coelenterata, Annuloida, Annulosa, Molluscoida, Mollusca, and Vertebrata. These series all differ more or less from one another, but a

[1] Newlands, *Chemical News*, July 30, 1864.
[2] Dumas, quoted by Newlands, *op. cit.*
[3] The newer atomic weights of Cs, Fl, Mg, and Ba do not correspond so exactly as their old ones with the sum of the other elements.
[4] *Chem. News*, Aug. 20, 1864, p. 94.

certain agreement is observed between their members, and similarly the **elements** may be arranged in **series.**

Mendelejeff points out, that if we take those elements having the lowest atomic weight, and omit hydrogen, between which and lithium there is a great gap, the seven elements, lithium, glucinum, boron, carbon, nitrogen, oxygen, and fluorine, may be regarded as typical elements forming a series representing the lowest members of seven groups. The next seven elements may be arranged in a similar way:—

Li = 7 : G = 9·4 : B = 11 : C = 12 : N = 14 : O = 16 : F = 19 :
Na = 23 : Mg = 24 : Al = 27 : Si = 28 : P = 31 : S = 32 : Cl = 35·5.

To each group of seven elements Mendelejeff gives the name of a **small period** or **series.** In each series the characters of the elements vary gradually and regularly as their atomic weights increase. This variation is periodical, *i.e.* varies in the same way in each series, so that the elements which have corresponding places in each series, correspond also to a certain extent in their properties, and form similar compounds. The atomicity is least in the first, and greatest in the last members of each series. Thus the first members of the series form monochlorides, the second dichlorides, the third trichlorides, and so on.

In the accompanying table R represents radical or element, and R^{i} indicates that the element is monatomic, so that one atom combines with one of Cl to form a monochloride, RCl. R^{ii} indicates that the element is diatomic, and so on.

But a difference is to be observed between the even and the uneven series. Corresponding members of even series, such as the fourth and sixth, agree with each other, and members of uneven series like the fifth and seventh agree. This agreement is greater than between the members of an even series, such as the fourth, and those of an uneven series like the fifth, although the fifth is more closely placed to the fourth than the sixth is. Thus Ca and Sr belonging to the fourth and sixth series have a greater resemblance to each other than they have to Zn or Cd, which belong to the fifth and seventh series, and these metals on the other hand have a greater resemblance to each other than they have to Ca or Sr. The members of even series are less metalloidal or more metallic than those of uneven series, *e.g.* Mn of the fourth series is less metalloidal than Br of the fifth series. In the even series the metallic or basic character predominates, whilst the corresponding members of the uneven series rather exhibit acid properties. The members of the even series, so far as we know, form no volatile compounds with hydrogen or alcohol radicals, while the corresponding members of the uneven series do form such compounds.

The last members of the even series resemble in many respects (in their lower oxides, etc.), the first members of the uneven series; thus chromium and manganese in their basic oxides are analogous to copper and zinc. But there are great differences between the last members of the uneven series (haloids), and the first members of the next even series (alkali metals). Now between the last members of the even series there occur, according to the order of atomic weights, all those elements which cannot be included in the small periods. Thus between Cr and Mn in the one series, and Cu and Zn in the next, there come the elements Fe, Co, Ni, and in a similar way after the sixth series come Ru, Rh, Pd, and after the tenth Os, Ir, Pt. Mendelejeff gives the name of a **long period** to two such series with three intervening members, forming seventeen in all.

From the difficulty of arranging all the elements in this system, it cannot be regarded as yet perfect, but the fact that Mendelejeff was able so correctly to foretell the properties of gallium, shows that it must contain a large element of truth. At the time that he drew up his table there was a blank in the third group of the fifth series.

The relationships of the metal which Mendelejeff believed would fill this

MENDELEJEFF'S CLASSIFICATION OF THE ELEMENTS.

Series	Group I. R^{i}_2O $R^{i}Cl$	Group II. $R^{ii}O$ $R^{ii}Cl_2$	Group III. $R^{iii}_2O_3$ $R^{iii}Cl_3$	Group IV. $R^{iv}H_4$ $R^{iv}O_2$ $R^{iv}Cl_4$	Group V. $R^{v}H_3$ $R^{v}_2O_5$ $R^{v}Cl_5$	Group VI. $R^{vi}H_2$ $R^{vi}O_3$ $R^{vi}Cl_6$	Group VII. $R^{vii}H$ $R^{vii}_2O_7$ $R^{vii}Cl_7$	Group VIII. — $R^{viii}O_4$ $R^{viii}Cl_8$
1	H = 1							
2	Li = 7	G or Be = 9·4	B = 11	C = 12	N = 14	O = 16	F = 19	
3	Na = 23	Mg = 24	Al = 27·3	Si = 28	P = 31	S = 32	Cl = 35·5	
4	K = 39	Ca = 40	— = 44	Ti = 48	V = 51	Cr = 52	Mn = 55	Fe = 56 Co = 54 Ni = 59 Cu* = 63
5	(Cu* = 63)	Zn = 65	—† = 68	— = 72	As = 75	Se = 78	Br = 80	
6	Rb = 85	Sr = 87	? Yt = 89	Zr = 90	Nb = 94	Mo = 96	— = 100	Ru = 104 Rh = 104 Pd = 106 Ag* = 108
7	(Ag* = 108	Cd = 112	In = 113	Sn = 118	Sb = 122	Te = 125	I = 127	
8	Cs = 133	Ba = 137	? Di = 138	? Ce = 140	—	—	—	— — — —
9	(—)	—	—	—	—	—	—	
10	(—)	—	Yb = 173	La = 180	Ta = 182	W = 184	—	Os = 199 Ir = 193 Pt = 195 Au* = 196
11	(Au* = 196	Hg = 200	Tl = 204	Pb = 206·5	Bi = 208	—	—	
12	—	—	—	Th = 231	—	U = 240	—	—

* Cu, Ag, and Au are included in Group I. on account of their forming cuprous, argentous, and aurous oxides, but on account of their resemblance in many respects to the metals in Group VIII. they are also included in it. † This blank has now been filled up by the discovery of gallium.

gap will be more easily seen by omitting the even series on either side of it, and taking only the odd series with which it will, as already mentioned, the more closely correspond.

Series.	Group II.	Group III.	Group IV.	Group V
3	Mg	Al	Si	P
5	Zn	—	—	As
7	Cd	In	Sn	Sb

As it stands between zinc with an atomic weight of sixty-five, and arsenic with one of seventy-five, while it is separated from the latter by a blank, its atomic weight must be about sixty-eight. As it is atom-analogous with Al, its salts should have a similar constitution. It should form an oxide x_2O_3, and a sulphide x_2S_3. It will be precipitated from its solution by ammonium sulphide. The metal should be easily reduced by carbon or sodium, it should have a specific gravity of 5·9, and decompose water at a red heat. As it belongs to an odd series, it should, like zinc, form volatile compounds with organic radicals, and form also anhydrous chlorides.

On the discovery of the metal gallium, it was found to agree in almost every respect with the prediction of Mendelejeff, and this fact is not interesting to chemists only, but also to pharmacologists. For the great **object of pharmacology** is to obtain such a knowledge of the relations between the physical and chemical characters of bodies, and their actions upon the living organism, that we may be able to predict their **actions** with certainty, and to know the modifications which alterations in their physical and chemical characters will produce on their physiological action.

Mendelejeff's present classification is imperfect, because we find that by it the members of some natural groups, such as those of the earthy metals, are separated from one another, although they agree in their chemical characters.

We find also that metals having similar pharmacological actions, as copper, zinc and silver, do not fall naturally together in this arrangement. But, on the other hand, we find also that by this classification, elements are brought together which do not at first seem to have any resemblance to each other, and are yet found by recent investigations to have a physiological connection. Thus mercury and calcium do not appear to resemble one another, yet Prevost has shown that, in acute poisoning by mercury, the calcareous matter disappears from the bones, and in the process of elimination by the kidneys produces calcification of these organs.[1]

Organic Radicals.—Whether the so-called elements be compounds or not, it is certain that several of them have the power of uniting with themselves and with others in such a way as to form bodies called compound radicals which resemble elements in many respects. These groups of atoms may enter into and again pass out of combination with other substances, just as elements do.

For example, when compounds of the elements unite, an interchange of elements takes place. Thus when calcium oxide (CaO) and hydrochloric acid (HCl) combine, the oxygen leaves the calcium to combine with the hydrogen and form water, while the chlorine leaves the hydrogen and combines with the calcium to form calcium chloride.

$$CaO + 2\,HCl = CaCl_2 + H_2O.$$

[1] Prevost, *Revue Médicale de la Suisse Romande*, p. 553, Nov. 15; p. 605, Dec. 15, 1882; p. 5, Jan. 15, 1883.

But when ethylic alcohol (C_2H_6O) is treated with hydrochloric acid (HCl), it is not oxygen which leaves the alcohol and is replaced by chlorine. The alcohol does not split up into the group C_2H_6 and the element oxygen, but into the two groups OH and C_2H_5.

$$C_2H_6O + HCl = C_2H_5Cl + H_2O\,;$$

or, as it may also be represented—

$$C_2H_5 \; OH + HCl = C_2H_5 \; Cl + H \; OH$$

To the group OH the name of hydroxyl has been given, and to the group C_2H_5 that of ethyl.

Similarly, when acetic acid ($C_2H_4O_2$) is treated with phosphorus trichloride (PCl_3) the three atoms of chlorine leave the phosphorus, and are replaced by three hydroxyl (OH) groups.

$$3\ C_2H_4O_2 + PCl_3 = 3\ C_2H_3OCl + PO_3H_3\,;$$

or, as it might be represented—

$$\left.\begin{array}{ll} C_2H_3O & OH \\ C_2H_3O & OH \\ C_2H_3O & OH \end{array}\right\} + P \left\{\begin{array}{l} Cl \\ Cl \\ Cl \end{array}\right. = \left.\begin{array}{ll} C_2H_3O & Cl \\ C_2H_3O & Cl \\ C_2H_3O & Cl \end{array}\right\} + P \left\{\begin{array}{l} OH \\ OH \\ OH \end{array}\right.$$

This mode of representation is awkward and cumbrous, although it is clear, and the same reactions may be represented more shortly thus:

$$3\ C_2H_3O.\ OH + PCl_3 = 3\ C_2H_3O.\ Cl + P\,.\,(OH)_3.$$

Here again it is not oxygen, but hydroxyl (OH), which breaks off from the acetic acid, just as it did from alcohol; but instead of the group C_2H_5 (ethyl) being left behind, we have another group, C_2H_3O (acetyl).

It is evident that such groups of atoms or radicals, as they are termed, as hydroxyl, ethyl, acetyl, &c., behave in combination just like elements. They are not known in a free state.

In order to exhibit the valency and probable relationships of radicals, they are sometimes expressed by graphic formulas, in which the affinities are shown by a —, as well as in the ways already shown.

As the position of the radicals in some compounds, *e.g.* in the organic alkaloids, is probably of great importance in regard to their action, although the subject is not well understood at present, the most important radicals are given below, with their graphic as well as their ordinary formula.

Hydroxyl, OH, or $-O-H$. This is a monad radical, consisting of one atom of dyad oxygen, $-O-$, with one of its

two affinities saturated by an atom of hydrogen, and the other affinity free. It was at one time called water-residue, as it is the residue left after the removal of one atom of hydrogen from water, which may be regarded as the hydride of the radical.

Hydroxyl is an important constituent of alcohols, regarding the chemical constitution of which two views may be taken. They may either be looked on as water in which one atom of hydrogen is replaced by organic radicals, or as compounds of the radicals with hydroxyl. The constitution of water and alcohol may be represented graphically, R standing for a monad organic radical—

$\mathrm{H-O-H}$ water;

$\mathrm{R-O-H}$ alcohol, *e.g.*, $\mathrm{Ethyl-O-H}$; $\mathrm{Phenyl-O-H}$

Ethyl-alcohol. Phenyl-alcohol, or Phenol.

The presence of the hydroxyl group in certain substances, and also its position in them,[1] appear to be of great importance in regard to their physiological action.[2]

By replacing the hydrogen in one atom of hydroxyl by a monad, or in two atoms by a dyad element, other radicals are formed, *e.g.*

Potassoxyl, KO, or $\mathrm{-O-K}$.

Zincoxyl, OZnO, or $\left.\begin{matrix}\mathrm{-O}\\ \mathrm{-O}\end{matrix}\right>\mathrm{Zn}$.

When united to carbonyl, hydroxyl forms a very important radical carboxyl.

Carbonyl, CO or $\mathrm{-\underset{\displaystyle O}{\underset{\|}{C}}-}$, is a dyad radical consisting of tetrad carbon, in which two affinities are saturated by dyad oxygen, and two left free. It exists in aldehydes, ketones, and acids, although in aldehydes it is combined with hydrogen, and in acids with hydroxyl, to form other radicals. In ketones both its free affinities are saturated by organic radicals, which may either be of the same kind or of different kinds.

$\mathrm{R-\underset{\displaystyle O}{\underset{\|}{C}}-R}$, *e.g.* $\mathrm{Methyl-\underset{\displaystyle O}{\underset{\|}{C}}-Methyl}$ $\mathrm{Phenyl-\underset{\displaystyle O}{\underset{\|}{C}}-Methyl}$

Acetone. Phenyl-methyl-acetone.

Aldehyde Group, CHO, or $\mathrm{-\underset{\displaystyle O}{\underset{\|}{C}}-H}$. When the free affinity

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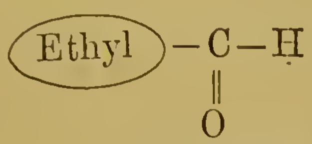
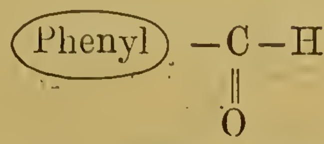
[1] Efron, *Pflüger's Archiv*, xxxvi. p. 467.
[2] Stolnikow, *Zeitschr. f. physiol. Chem.*, 1884, viii. pp. 235 and 271.

of this group is saturated by a monatomic radical, we get aldehydes; thus—

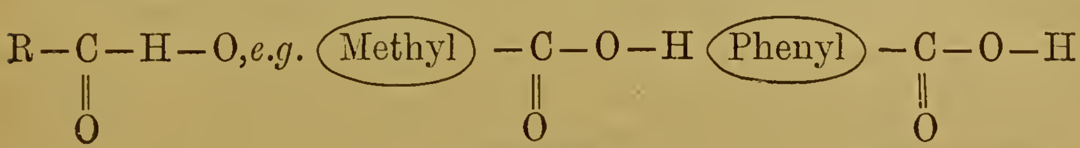


Ethyl-aldehyde.

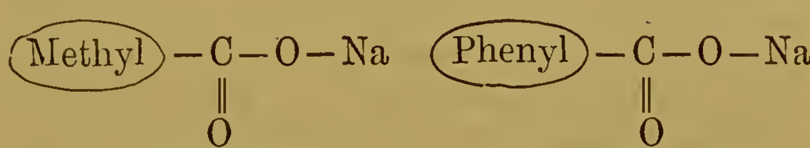


Benzoic aldehyde (oil of bitter almonds).

Carboxyl, CO.OH, or $\left.\begin{matrix}CO\\H\end{matrix}\right\}O$, or $-\underset{\overset{\|}{O}}{C}-O-H$. This is a monad radical. When its free affinity is saturated by an organic radical, it forms monad organic acids, in which the hydrogen of the hydroxyl is readily replaced by a basic element.

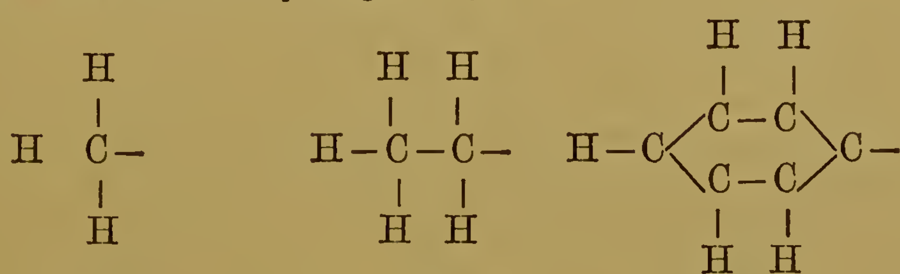


Acetic acid. Benzoic acid.



Sodium acetate. Sodium benzoate.

Carbon forms an immense number of radicals by union with itself and with hydrogen, *e.g.*



Methyl. Ethyl. Phenyl.

Nitrogen gives origin also to a number of most important radicals.

Nitroxyl, NO_2.

Amidogen, NH_2, or $-N\begin{matrix}\diagup H\\ \diagdown H\end{matrix}$.

Imidogen, NH or $N\begin{matrix}\diagup H\\ \diagdown\end{matrix}$.

Phosphorus, arsenic, and **antimony** give origin also to a number of radicals similar to those of nitrogen.

$$PH_2, \text{ or } -P{<}^{H}_{H};\quad SbH_2, \text{ or } -Sb{<}^{H}_{H};\quad AsH_2, \text{ or } -As{<}^{H}_{H}$$

$$PH, \text{ or } -P{<}^{H}_{\diagdown};\quad SbH, \text{ or } -Sb{<}^{H}_{\diagdown};\quad AsH, \text{ or } -As{<}^{H}_{\diagdown}$$

Sulphur also gives origin to some important radicals.

Sulphuryl (sulphon), SO_2, or $>S{<}^{O}_{O}$; Sulphin, SO, or $-S{<}^{\!/\!/O}_{\diagdown}$

Chemical Reactions and Physiological Reactions.—Each element and each of its compounds has chemical reactions special to itself, by which it can be recognised and distinguished from all others. The number of these chemical reactions is therefore very great, but there are a few reactions which are common to a great number of the elements. We shall find that something similar occurs in their physiological reactions.

The number of possible actions which may be exerted on the body by the elements and their compounds is very great, yet we shall find that there are certain physiological reactions which are common to so many that their repetition under the head of each drug becomes monotonous.

Chemical Reactions.—Although the chemical reactions of the metallic elements are numerous and varied, yet there are certain reactions which are common to a very large number, and by these the class of metallic elements may be subdivided into sub-classes. Other reactions again are common to a few elements only, and by these the sub-classes may be subdivided into groups. Other reactions again are peculiar to each individual element, and by them it may be distinguished from all others.

Thus, by the use of hydrogen sulphide, or ammonium sulphide, we at once divide the class of metallic elements into two sub-classes:

A. Metals which give a precipitate with one or other of these reagents.

B. Metals which give no precipitate with either.

Physiological Reactions.—It is probable that, if our knowledge of physiological chemistry were sufficient, we might be able to classify physiological reactions according to the chemical relation between substances introduced into the organism and the various constituents of the organism itself. At present we

are quite unable to do this; but, as albuminous substances form an essential part of all living organisms, we may roughly divide the elements physiologically, by their relation to albumen, just as we do it chemically, by their relation to sulphur, into two sub-classes:

A. Those which precipitate albumen.

B. Those which do not.

Just as in the case of sulphides, we might further sub-divide sub-class A into two sections:

(*a*) Those which precipitate albumen in acid solutions.

(*b*) ,, ,, ,, in neutral or alkaline solutions.

Section (*b*) may be further sub-divided into groups according to the kind of albuminous bodies which its members precipitated, *e.g.*, myosin, globulin, serum-albumen, albumoses, peptones, &c.

We might also divide sub-class B in two sections:

(*a*) Substances which, though they do not precipitate albumen, have a marked affinity for fatty substances or other constituents of the organism, and especially of the nervous system (p. 144).

(*b*) Substances having no such action.

It is evident that such a classification as this, although it might form the groundwork of a system to be perfected at some future time, is at present so imperfect that it is generally more convenient to divide physiological reactions according to the organs affected: e.g., muscles, nerve-centres, respiration, circulation, secretion, &c.

A. This group contains substances which **paralyse muscles** and **motor nerves.** The number of these substances is very great (p. 126 *et seq.*, p. 150).

This large group can again be subdivided into those which (*a*) paralyse muscle, while affecting the nerves but slightly, or (*b*) paralyse the nerves and leave the muscle uninjured.

B. Another large group is that which acts specially on **nerve-centres**, and has little effect either on muscles or motor nerves. This contains sub-groups of substances which affect the brain, medulla, or spinal cord by exciting, paralysing, or disturbing the functions of each.

C. Another group is that which affects the **secretions**, with sub-groups of substances affecting the secretions from the sweat and mammary glands, salivary, gastric, or intestinal glands, liver, or kidneys.

D. Another group still is that which acts chiefly upon the **circulation.**

These groups are all more or less distinct, although they, to a certain extent, may run into, or overlap, each other.

Individual members of the same group may differ very widely in their physiological action, even when they all finally paralyse

muscle, nerves, and nerve-centres. For while they may produce the same final result, the course of their action will be different, and the symptoms they occasion will depend very greatly upon the part of the organism which they affect first. Thus atropine and curare both completely paralyse motor or efferent nerves, but, while a very large dose of curare is required to paralyse the cardiac and vascular nerves, a very small dose paralyses those going to the muscles, and produces increasing weakness, gradually passing into death. On the other hand, an enormous dose of atropine is required to paralyse the motor nerves of muscles, but very small doses are sufficient to affect the nerves of the heart and other involuntary muscles, and thus we get rapid circulation, dilated pupil, and restless delirium.

The physiological action of any drug depends to a great extent, not merely on its general affinities for classes of tissues, but upon its particular affinity, or power of acting on one tissue or organ first. The organ first affected may, through its functional activity, greatly alter the effects of the drug upon the others.

As an example of this we may take the effects produced by very large and by moderate doses of veratrine on the frog. A moderate dose will produce great stiffness of the muscles, while a very large dose may have comparatively little effect. Yet if the large dose were applied directly to the muscles it would act more powerfully than the moderate dose. The reason that it does not do so in the living body is that the large dose paralyses the heart so quickly that the circulation stops, and therefore the poison, not being conveyed to the muscles, has no action upon them.

Relation between Isomorphism and Physiological Action.—From a number of experiments made by Dr. Blake, he concluded that when inorganic salts were injected directly into the circulation, the intensity of their physiological action increased in proportion to their molecular weight, but only in those groups of elements where the salts were isomorphic, or in other words, crystallised in the same forms. Thus groups whose salts were crystallised in different forms had quite different physiological actions. He adopts Mitscherlich's division of the elements into nine groups, and considers that the physiological action of the different groups differs in kind, whilst that of the individual members of the same group agrees in kind but differs in degree. Thus he states [1] that the salts of the first group increase in activity in the order mentioned, silver being the most active, and lithium the least.

[1] Blake, *American Journal of Science and Arts*, vol. vii., March 1874 (corrected reprint).

These groups are as follows:—

Group 1. Lithium, sodium, rubidium, thallium, cæsium, and silver. According to him they produce death by acting on the lungs and impeding the pulmonary circulation. None of them affect the nervous system excepting cæsium; nor do any affect the pulmonary circulation excepting silver.

Group 2. Magnesia, ferrous salts, manganous salts, nickel, cobalt, copper, zinc, and cadmium are increasingly lethal in the order mentioned. They kill by arresting the action of the heart.

Group 3. Beryllium, alumina, yttria, cerium, and ferric salts both impede the systemic and pulmonary circulation.

Group 4. Calcium, strontium, barium, and lead salts kill by paralysing the ventricles of the heart.

Group 5. Palladium, platinum, osmium, and iridium act on the heart, respiration, circulation, and blood.

Group 6. Ammonia and potash paralyse the heart and cause convulsions.

Group 7. Hydrochloric, hydriodic, bromic, and iodic acids impede the circulation and kill by arresting the circulation.

Group 8. Phosphoric acid, arsenic acid, and antimony kill by arresting the pulmonary circulation.

Group 9. Sulphuric and selenic acid impede the pulmonary circulation.

The author's statements regarding the mode of action of the elements show that their physiological action has not been fully investigated, and his results as to the lethal dose are probably only approximate and may want re-investigation; but while we cannot accept at present all his results or conclusions as final, yet his last and chief conclusion is one of great interest—viz., that in living matter we possess a reagent capable of aiding us in our investigations on the molecular properties of substances.

Relation between Spectroscopic Characters and Physiological Action.

The quickness with which a pendulum oscillates is less or greater according to its length, a long one oscillating slowly, and a short one quickly. The vibrations of a string or pipe are also slow or quick, and the note which it yields is low or high, according as it is long or short.

Similarly, according to Lecoq de Boisbaudran, the rate of vibrations of molecules, and the wave-lengths of the light which they emit, are determined by their weight. When the molecular weight is high, the vibrations of the molecules are slow, and the light which they emit has long wave-lengths, and is situated towards the red end of the spectrum. When the weight is low the vibration of the molecules is rapid; and the light they emit lies towards the violet end of the spectrum.

In the same family of elements the mean length of the wave of light which they emit is a function of their atomic weight, so that for bodies of the same chemical type the general form of the spectrum persists, but is gradually modified by the mass of the molecules. As the atomic weight diminishes, the spectrum will tend to ascend towards the violet, and as it increases the spectrum will tend to descend towards the red.

Until recently, our observations on the spectra of bodies were limited to the visible spectrum, but the application of photography now enables us to extend our observations both above and below the visible spectrum, and to ascertain the presence of definite spectra in the ultra-red and ultra-violet, when nothing of the sort is visible to the eye. In most musical sounds besides the fundamental note we have a number of harmonics having a much greater rapidity of vibration than it. Similarly, in the spectrum there appear harmonics as well as the fundamental spectral lines, and so instead of one

line or band there may be a number. According to the author already quoted, the corresponding harmonics in a series of analogous spectra have mean wave-lengths which increase in proportion to the weight of the molecules.

It might appear, therefore, that a relation might be observed between the spectroscopic characters and physiological action of an element, and this idea was propounded by Papillon. His idea was, however, to a great extent based on the experiments of Rabuteau referred to later on, and just as no definite relation can be at present traced between the atomic weight and the toxic action of a metal, so no definite relation can be observed between its spectroscopic characters and its physiological action.

Further consideration, however, will show us that this is not at all to be wondered at, for in physiological experiments we are not working with the same molecules which yield the spectrum.

In spectrum-analysis, when line spectra are in question, according to one view we are in presence of phenomena produced by the chemical atom, whereas this atom exists only molecularly combined at lower temperatures. According to another view, that put forward by Lockyer, we are in presence of phenomena produced by a series—possibly a long series—of simplifications, brought about by the temperature employed, and this simplification can begin at very low temperatures, and is indeed indicated by Dalton's law of multiple proportions.

Such molecular simplifications and differences are represented by ozone and oxygen, ordinary and amorphous phosphorus, the various forms of sulphur and so on, and it is therefore at this lower range of temperature—where the phenomena are to be studied by absorption, and not by radiation—that we must look for connections between molecular structure and physiological action if any such connection exists.[1]

Some of the absorption bands which occur in the spectra of bodies at ordinary temperatures may be in the visible spectrum, like those observed in alcoholic and aromatic substances;[2] but others may be quite invisible, and only recognisable by the aid of photography in the ultra-red or ultra-violet.[3]

Relation between Atomic Weight and Physiological Action.

From experiments made on the toxic action of the chloride, bromide, and iodide of potassium, Bouchardat and Stewart Cooper came to the conclusion that a relation existed between the physiological activity of elements and their atomic weight, the activity being inversely as their atomic weight, *e.g.* fluorine (atomic weight, 19) being more active than chlorine (atomic weight, 35·5).

In 1867, Rabuteau made a number of experiments from which he concluded that Bouchardat was correct in saying that the physiological activity of the monatomic metalloids was in inverse proportion to their atomic weight, while that of the diatomic metalloids increased directly with their atomic weight: selenium being more active than sulphur.

He considered also that he had discovered a new law regarding the relation between the atomic weight and the physiological activity of metals: viz., that the activity of metals increases with their atomic weight. He afterwards qualified this statement by saying that the poisonous action increased with the atomic weight amongst elements belonging to the same group. Thus potassium (atomic weight, 39) is more poisonous than sodium (23), and barium (137) than calcium (40). But it has been shown by Husemann that lithium is much more poisonous than sodium, and his results have been confirmed by Richet.

In the following table the lethal activity of various metals is given as

[1] *See* Hartley, *Phil. Trans.*, Part II. 1885.
[2] Russell and Lapraik, *Journ. Chem. Soc.*, April 1881.
[3] Abney and Festing, *Phil. Trans.*, 1882, p. 887.

determined by Richet, and of the metals belonging to the groups of the alkalis and earths as determined by Richet, by Cash and myself, and by Botkin, jun. Where the position of the metals in the tables is different the symbols are printed in italics. The most active, Hg, is first; the least active, Na or Ca, last.

Richet	Brunton and Cash	Botkin, junr.	Atomic Weight	Richet	Brunton and Cash	Botkin, junr.	Atomic Weight
Hg	—	—	200	—	Cs	Cs	133
Cu	—	—	63·4	Li	Li	Li	7
Zn	—	—	65	Mn	—	—	55
Fe	—	—	56	*Ba*	—	—	137
Cd	—	—	111·2	Mg	—	—	24
NH_4	—	—	18	—	La	—	139
K	K	K	39	—	Di	—	145·4
—	Be	—	9	—	Er	—	166
—	Rb	Rb	85·3	Sr	Sr	—	87·4
Ni	—	—	58	—	Yt	—	89·8
Co	—	—	58	*Ca*	*Na*	—	40 | 23
—	*Ba*	—	137	*Na*	*Ca*	—	23 | 40
—	*NH_4*	—	18				

Richet's experiments were made upon fish, and the substances were added to the water in which the animals were swimming. The experiments of Cash and myself were made upon frogs, and the substances were injected subcutaneously. Botkin's experiments [1] were made upon dogs, and the substances were injected directly into the circulation.

It is possible that the differences observed were due to the differences in the animals on which the experiments were made, or in the way of applying the poison. Botkin's table, so far as it goes, agrees perfectly with Cash's and mine, and there is a general correspondence also between Richet's results and ours, although there are several differences in particulars.

It is thus evident that the relationship between atomic weight and physiological action is no simple one. But indeed, on looking into the matter more closely, we could hardly expect it would be. For the toxic action of an element may depend upon its effect on the muscles, nerves, nerve-centres, blood, or on the digestive or excretory systems. These differ from one another in their composition, and while it is possible that the elements belonging to a certain group may have relations varying with their atomic weight to individual organs or structures, we can hardly expect those relationships to be the same to all organs.

Thus an element with one atomic weight may prove fatal, by affecting the muscular power of an animal, while another with an atomic weight either higher or lower, may be still more deadly by affecting the nervous system or heart.

What we want, therefore, is not a general relationship between atomic weight and toxic action, but a knowledge of the particular relationships of each group of elements to each organ and tissue of the body.

Relation of Atomic Weight and Smell.

The idea has been put forward by Ramsay that the sense of smell is excited by vibrations of a lower period than those which give rise to the sense of light or heat. These vibrations are conveyed by gaseous molecules

[1] S. Botkin, junr.: 'Zur Frage über den Zusammenhang der physiologischen Wirkung mit den chemischen Eigenschaften der Alkalimetalle der ersten Gruppe nach Mendelejeff,' *Centralb. für die med. Wissenschaft.* No. 48 1885.

to the surface network of nerves in the nasal cavity. The difference of smells is caused by the rate and by the nature of such vibrations, just as difference in tone of musical sounds depends upon the rate and on the nature of the vibration—the nature being influenced by the number and pitch of the harmonics. Just as the eye and ear are capable only of appreciating sight or sound vibrations occurring within a limited range, so the nose is unable to appreciate a smell the result of the rapid vibrations produced by substances of low molecular weight. Hydrocyanic acid appears to be at the lowest limit, as one in five are, according to him, unable to detect its odour. It is fifteen times the molecular weight of hydrogen, and he concludes that to produce the sensation of smell a substance must have a molecular weight at least fifteen times that of hydrogen. The intensity of smell in bodies of similar constitution increases with the molecular weight; thus, methyl-alcohol is odourless, but the intensity of smell increases with the molecular weight of each succeeding member of the alcohol group, until the limit of volatility is reached, and they become changed into solids with such a low vapour tension that they give off no appreciable amount of vapour at the ordinary tension.[1]

Relation of Atomic Weight to Taste.

Haycraft considers[2] that 'quality' in taste depends upon the nature of the atoms found in the sapid molecule. A study of the periodic law demonstrates that similar tastes are produced by combinations which contain elements such as lithium, sodium, potassium, which show a periodic recurrence of ordinary physical properties. Among the carbon compounds, those which produce similar tastes are found to contain a common 'group' of elements. Thus organic acids contain the group CO.OH, the sweet substances CH_2.OH. There is no relation between quality of sensation and gross molecular weight, except that substances of either very small or very great molecular weight are not tasted at all.

Connection between Chemical Composition and Physiological Action.

In considering this subject and other subjects allied to it, we must carefully distinguish between chemical composition and chemical constitution; between the mere elements of which a compound is formed and the manner in which these elements are put together. Thus the cyanides, or nitriles, and the isonitriles, or carbamines, both contain carbon and nitrogen, and contain them in equal proportions; but the manner in which the carbon is united with the nitrogen probably differs in the two classes, and their physiological action is different. Their chemical composition is the same, but their chemical constitution is different.

It was pointed out by Blake in 1841 that a close connection exists between the chemical constitution and physiological action of salts; their physiological action on animal organisms appearing to depend chiefly on the base. Yet the physiological action of any salt is not dependent entirely upon the base. It may be, and sometimes is, modified to a very great extent by the acid; moreover, we find that the salts which the same inorganic base

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[1] *Nature*, June 22, 1882, p. 187.
[2] *Ibid.*, Oct. 8, 1885, p. 562.

may form with different acids may present very different physiological actions, as in the case of the carbonate, bromide, and cyanide of potassium. The same is the case with organic bases, and Richardson, in 1865, drew attention to an example of the relation between the action of the base and acid in the amyl compounds. He found that amyl-hydride had an anæsthetic effect; the introduction of oxygen, as in amyl-alcohol or amyl-acetate, added spasm to this action; amyl-iodide produced a large excretion of fluid from the body, while amyl-nitrite had a great effect on the circulation. Thus, the base remaining the same, different acid radicals modified the action of the compound.[1]

The fact is that sometimes the action is determined chiefly by the base (whether it be inorganic or organic), and sometimes chiefly by the acid. The action of the whole salt may differ to a great extent from that of the substances composing it, and it may agree to some extent with other salts, which differ from it both in regard to the base and acid composing them; thus—the sulphate of magnesium and the sulphate of sodium are both purgative, and in this property they agree not only with the sulphate of potassium, in which the base is different although the acid is the same, but with the bitartrate of potassium, in which both the base and the acid are different. This fact confirms what has already been said regarding the necessity for taking into consideration crystalline form and physical aggregation, as well as chemical composition (p. 15).

Physiological Action of the Constituents of a Drug.—In the case of acids and bases, the physiological action of each is modified by their union, *e.g.* when caustic soda and hydrochloric acid unite, the caustic action of each is destroyed, and we obtain sodium chloride and water, which have different physiological actions, as well as different chemical characters, from either the acid or the base.

But if we examine a series of salts of the same base with different acids, or of the same acid with different bases, we find that both the acid and the base modify the physiological action of the compound.

Different Acids.

Sodium	hydrate	*caustic.*
,,	bicarbonate	*antacid.*
,,	sulphate	*purgative.*
,,	benzoate	*antilithic.*
,,	salicylate	*antipyretic.*
,,	cyanide	*powerful poison.*

Different Bases.

Sodium	chloride	*neutral in action.*
Potassium	,,	*muscular poison.*
Zinc	,,	*caustic.*
Barium	,,	*muscular poison.*
Silver	,,	*inert.*
Iron	,,	*astringent, hæmatinic.*
Mercuric	,,	*corrosive, antiseptic.*

This modification is in some cases due to a change in the

[1] *Brit. Assoc. Reports*, 1865, p. 280.

physical conditions, and especially in the solubility of the compound. Thus the chloride of silver is inert so long as it remains in the form of a chloride, because it is insoluble. It thus differs much from the corrosive chloride of zinc, while if we were to compare the action of the nitrate of silver and zinc we should find considerable similarity.

Another cause of difference is the different **proportion of the acid to the base.**

Thus the proportion of sodium (Na=23) to the acid radical in the following sodium salts is as follows: in the hydrate as 23 to 18; in the bicarbonate as 23 to 61; in the sulphate as 23 to 96; in the benzoate as 23 to 121; in the salicylate as 23 to 137.

In this connection, too, the degree of **saturation of the acid** by the base must be considered. If, for example, the acid is not saturated, part of the action of the compound is due to its acid chemical properties; and if, on the other hand, a weak acid be combined with a strong base, this action is partly due to the alkaline chemical property.

Relation between Physiological Action and Chemical Constitution.

An immense step has been made of late years in our knowledge of the relation between chemical constitution and physiological action by the discoveries of Crum-Brown, Fraser, and Schroff, who have shown that by modifying artificially the chemical constitution of a drug it is possible to modify also its physiological action. And not only so, but they have shown that similar modifications in the chemical constitution of various drugs induce similar modifications in the action of their derivatives; thus they have found that by introducing methyl into the molecule of strychnine, brucine, and thebaine, the convulsive action exerted by these substances on the spinal cord was changed into a paralysing one exerted on the ends of the motor nerves. Other alkaloids, also, which do not exhibit a convulsive action, nevertheless exhibit a paralysing one when their constitution is altered by means of methyl; thus methyl-codeine, methyl-morphine, methyl-nicotine, methyl-atropine, methyl-quinine, methyl-veratrine, and several others, all exhibit this paralysing action (p. 150).

As a general rule, most of the compound radicals formed by the union of amidogen with the radicals of the marsh-gas series possess a paralysing action on motor nerves.

The subject of the connection between chemical constitution and physiological action is the most important one in pharmacology, and we shall have to return to it in considering the actions of various groups of organic substances.

CHAPTER II.

CIRCUMSTANCES WHICH AFFECT THE ACTION OF DRUGS ON THE ORGANISM.

One of the most important circumstances affecting the action of any drug is the mode in which it is brought into contact with the various parts of the organism.

Local and Remote Action.—The **local** action of a drug is that which it exerts on the part to which it is applied. Thus sulphuric acid has a direct irritant or destructive action, and when applied to the skin or mucous membrane will produce local redness, inflammation, or sloughing. When swallowed, it produces weakness of the circulation, stoppage of the heart, and death.

This effect on the circulation is not due to the direct action of the acid upon the heart, the vessels, or the nervous system, after its absorption: it is due to the reflex action exerted upon them by the irritation of the nerves of the stomach which the sulphuric acid produces. This action on different parts through the nervous system is termed its **remote** action, in contradistinction to the local action of the acid upon the gastric mucous membrane.

The Interaction of various functions in the body is one of the greatest difficulties in the way of our readily understanding the action of drugs.

One function alters another, and the second reacts upon the first, so that in some cases it is almost impossible to say precisely how far the alteration in any function is due to the direct effect of the drug upon it, and how far to some indirect action. Thus curare when applied to a wound usually kills without producing any convulsion whatever. It paralyses the ends of the motor nerves, so that all the muscles in the body become powerless. But when it is given by the stomach, and excretion through the kidneys prevented, death is preceded by convulsions. These convulsions are not caused by any direct irritating action of the curare itself upon the nerve-centres; they are due to irritation of these centres by a venous condition of the blood. This venosity of the blood is due to imperfect respiration, produced by paralysis

of the respiratory muscles through the action of curare on the motor nerves.[1]

The effect of curare is a purely paralysing one, both when the animal dies quietly and when it dies with convulsions. In both cases it paralyses the motor nerves of the respiratory muscles and of the extremities. In both cases it causes death by arresting the respiration and producing asphyxia. But in the latter case the motor nerves of the extremities being only partially paralysed when asphyxia occurs, they respond by convulsive movements to the irritation of the nerve-centres, which the venous blood produces. In the former, the paralysis of the limbs being complete, the muscles remain perfectly quiet, notwithstanding the irritation of the nerve-centres.

Convulsions also sometimes occur previous to death from narcotic poisons: and in a description of the action of these poisons we frequently meet with the phrase, 'coma, convulsions, and death.' In such cases the convulsions are also caused by the irritation of the nerve-centres by asphyxial blood.

The drug causes the coma; the coma causes imperfect respiration; imperfect respiration renders the blood venous; and the venous blood causes convulsions.

Direct and Indirect Action.—The **direct** action of a drug is the effect it produces on any organ with which it comes in contact. Thus sulphuric acid applied to the skin, or taken into the stomach, will, according to its degree of concentration, irritate or destroy the mucous membrane which it touches. Its *direct* action upon them is therefore that of an irritant or caustic.

Curare, when applied to the ends of a motor nerve in a muscle, paralyses them. It does this either when the muscle is soaked in a solution of curare, or when the curare is carried through the substance of the muscle by means of the blood circulating in it.

Paralysis is therefore the direct effect of curare on the motor nerves.

The convulsions which sometimes occur in poisoning by curare are caused by its **indirect** action. It has no stimulating effect on the nerve-centres, when applied to them directly or caried to them by the blood, but by paralysing the muscles of respiration, and thus causing asphyxia, it indirectly irritates the nerve-centres, and causes convulsions.

Selective Action of Drugs.—Drugs sometimes seem to affect only one part of the body and to leave the other organs unaffected; although the drugs may be carried equally by the blood to every part of the body, they appear to combine with some and not with others. Many dye-stuffs will not attach

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[1] Hermann, *Arch. f. Anat. u. Physiol.*, 1867, 64, 650.

themselves to cotton fabrics, but will do so readily to wool or silk; and we find that different tissues, and even different parts of the same tissue, have very unequal attractions for stains: thus some anilin colours will deeply stain a nucleus, while leaving the cell in which it is contained entirely uncoloured. Although the different organs of the body contain many substances in common, yet their chemical composition varies within wide limits, and the products of the tissue-waste are also different. Even in the same organs the cells may have different properties, and even individual parts of the same cell may differ. Some have a reducing, and others an oxidising action; some an alkaline, and others—as may be ascertained from their action on anilin colours [1]—an acid, reaction (p. 70). We would therefore expect that, just as the tissues exert a selective action upon dyestuffs which we are able to see, they will also have a selective action on many organic substances, although this action may not be visible to our senses.

Primary and Secondary Action.—I have already stated (p. 5) that the so-called action of a drug is not one-sided: it is the reaction between the drug and the organism. While drugs are circulating in the body they may modify the chemical nature and the physiological functions of various organs. In some cases the drug, after doing this, may again leave the organs and be eliminated without undergoing any essential change; but in other cases the chemical character of the drug itself undergoes an essential change during its sojourn in the body. Some organic substances undergo complete combustion, and are converted into carbonates, while others are converted into substances having a powerful physiological action, but perfectly different from that of the substance originally introduced into the body. These products of the decomposition of the drug may then, while circulating in the blood, or during the process of excretion, exert upon the organism a marked physiological action quite different from that of the original substance. Perhaps one of the most marked examples of this is to be found in morphine. Morphine lessens the irritability of nerve-centres, producing sleep, and having a marked sedative action upon the stomach in allaying vomiting, either when introduced directly into the stomach or injected into the circulation. This is its primary action; but in the body morphine undergoes certain alterations and becomes partly converted into oxy-dimorphine, which appears to counteract the soporific action of morphine, and probably either oxy-dimorphine or some other product of the decomposition of morphine has an emetic action. The effect of these secondary products will manifest itself after the original

[1] P. Ehrlich, 'Ueber die Methylenblaureaction der lebenden Nervensubstanz.' *Deutsche med. Wochenschrift*, 1886, No. 4. *Ibid.* 1885.

dose of morphine has either been eliminated or undergone conversion into the products already mentioned; and thus the secondary action will be quite different from the primary, and instead of narcosis and quietness of the stomach, there will be excitement, and nausea or vomiting, which may require to be again counteracted by a larger dose of the original drug.

It is evident that the relation between the primary and secondary effects of a drug will, if this explanation be correct, vary very much according to the relative solubility of the drug originally administered, and of the products of its decomposition. If the products of decomposition be more soluble, and more readily eliminated, than the drug itself, they will leave the organism before it, and their action will hardly appear; but if they are less soluble, and more slowly eliminated, their action may persist for a considerable length of time.

Relation of Effect to Quantity of the Drug.—The effect of drugs varies very much according to the quantity employed. Sometimes this is due to the interaction of different parts of the body on one another, as already mentioned in regard to veratrine (p. 26). Sometimes it is due to the different effects upon individual cells or tissues. Thus we find, very generally, that any substance or form of energy, whether it be acid or alkali, heat or electricity, which in moderate quantity increases the activity of cells, destroys it when excessive.

But varying doses do not always produce opposite effects. We sometimes find that exceedingly small and exceedingly large doses have a similar effect, which differs from that produced by moderate doses. Thus very minute quantities of atropine render the pulse somewhat slow; larger quantities make it exceedingly rapid, and very large quantities again render it slow.

Moderate quantities of digitalis slow the pulse, larger quantities quicken it, and still larger quantities render it slow again. We find a similar effect produced by variation in temperature. Great cold disturbs the mental faculties, so that men exposed to it present symptoms which cannot be distinguished from those of intoxication. Ordinary temperatures do not disturb the functions of the brain, but high temperatures do, as we see in the delirium of fever, which in many cases immediately ceases when the temperature of the patient is reduced by cold baths.

Homœopathy.—This opposite action of large and small doses seems to be the basis of truth on which the doctrine of homœopathy has been founded. The irrational practice of giving infinitesimal doses has of course nothing to do with the principle of homœopathy—*similia similibus curantur:* the only requisite is that mentioned by Hippocrates, when he recommended mandrake in mania; viz. that the dose be smaller than would be

sufficient to produce in a healthy man symptoms similar to those of the disease. Now in the case of some drugs this may be exactly equivalent to giving a drug which produces symptoms opposite to those of the disease; and then we can readily see the possibility of the morbid changes being counteracted by the action of the drug, and benefit resulting from the treatment. For example, large doses of digitalis render the pulse extremely rapid, but moderate ones slow it.[1] The moderate administration, when there is a rapid pulse, is sometimes beneficial: this might be called *homœopathic* treatment, inasmuch as the dose administered is smaller than that which would make the pulse rapid in a healthy man; but it might also be called *antipathic*, inasmuch as the same dose administered to a healthy person would also slow the pulse.

Homœopathy can therefore not be looked upon as a universal rule of practice, and the adoption of any such empirical rule must certainly do harm by leading those who believe in it to rest content in ignorance instead of seeking after a system of rational therapeutics.

Dose.—The amount of a drug, which actually comes in contact with and affects the tissues, depends upon several conditions —(1) the **quantity** actually given; (2) its **proportion** to the body-weight; (3) the rapidity of its **absorption** by the blood from the place of introduction; (4) the condition of the **circulation** in various parts of the body, which determines the quantity of the drug carried to each; (5) the rate of its absorption by the **tissues**; (6) the rapidity of **excretion.**

The word **dose**, as employed in medicine, usually means the quantity given at one time, but sometimes this may be very different from what actually produces any effect. It is the amount of the drug existing in the blood at any given time, or rather the proportion of it that actually comes in contact with or is absorbed by the tissues, which really acts. We must therefore consider more in detail the circumstances which affect this proportion.

Size.—As the action which a drug has on the body is not dependent on its absolute amount, but on the proportion it bears to the body on which it is to act, an amount which is a small dose for one person is a very large one for another.[2] Thus if a grain of some active substance be injected at the same time into the veins of a full-grown man and into those of a boy of only half his weight, it will be distributed through twice as much blood in the man as in the boy, and each tissue will only receive half as much of it. The dose of a drug must therefore be regulated by the weight of the patient; and thus women, being

[1] *Vide* Traube, *Med. Centr. Ztg.* xxx. p. 94, 1861, and Brunton *On Digitalis*, p. 21.

[2] Buchheim, *Arzneimittellehre.* 3rd edit. p. 54.

lighter, require a smaller amount than men, and children less than adults. Though it would be more exact, it is not always convenient, to weigh patients; but in experiments on animals we usually weigh the animal carefully, and describe the dose in terms of the body-weight. For example, in describing the lethal dose of physostigmine we do not say that it is so many grains for an animal, but that it is 0·04 grain per pound weight of a rabbit. This relation, however, is not always an exact one, and other circumstances must be taken into account. Thus the **species** of the animal must be considered, for the same dose which would kill one kind of animal will not kill another. In animals of the same species the state of **nutrition** must be taken into account, for two animals of the same species, which would be nearly of the same size when equally nourished, may have very different weights if the one is fat and the other is lean. But the fat is a comparatively inert tissue, and if we give to each animal a dose regulated by its body-weight, the vital organs, brain, heart, and spinal cord of the fat animal will get a larger share in proportion than those of the lean one.

In testing the action of poisons on frogs, also, it must be remembered that a female frog with a quantity of spawn will be very heavy, but the spawn, like the fat, is not to be reckoned as tissue; so that a dose given in proportion to the actual weight would be much larger than the same proportion given to the frog after spawning.

Mode of Administration.—If a substance be **injected** into the **veins**, the whole of it mixes with the blood and becomes active immediately, and the maximum effect is thus at once obtained and will again diminish as the substance is excreted. But the case is different if it be injected **subcutaneously**, and if it be given by the **stomach** or any other **mucous cavity** the difference is still greater; for as soon as some of it is absorbed excretion begins, and thus one portion of the drug is passing out of the blood while another portion is being taken in. The amount in the blood is, then, only the difference between that absorbed and that excreted in a given time (Fig. 6). Absorption may be so slow, or excretion so quick, that there is never a sufficient amount of the substance in the blood to produce any effect. Thus Bernard found that a dose of curare which would certainly paralyse an animal when injected into the veins, or even subcutaneously, would have no effect when introduced into the stomach;[1] and showed that this was due to the kidneys excreting the poison as fast as it was absorbed from the stomach, by extirpating the kidneys,[2] when the animal became paralysed as surely as if the poison had been introduced at once into the

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[1] Bernard, *Leçons sur les Effets des Substances Toxiques*, p. 282.

[2] Bernard, *Revue des Cours Scientifiques*, 1865.

veins, though not so quickly. Hermann also discovered, without being acquainted with Bernard's observations, that curare taken into the stomach would produce paralysis if excretion were prevented by ligature of the renal vessels.

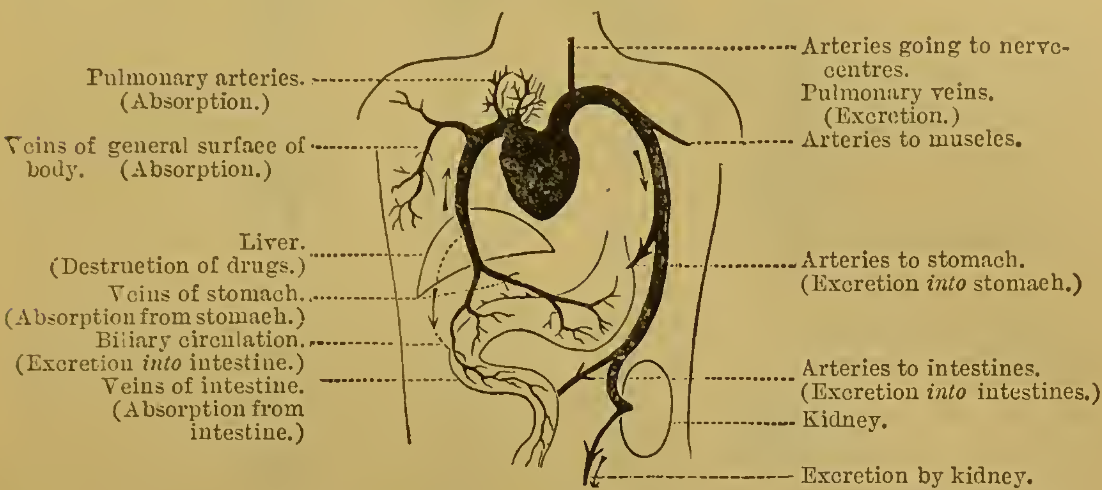

FIG. 5.—Diagram to illustrate absorption and excretion. The arrows show the direction of the currents. The absorbents from which the blood passes directly into the general circulation are represented diagrammatically by the veins of the lungs and of the general body surface in the figure. The absorbents by which the drug must pass through the liver, and possibly be partly excreted or destroyed, are represented by the veins of the stomach and intestine. The excreting channels by which the drug may pass directly from the body without re-absorption occurring are represented by the vessels of the lung and by the ureter. Those by which excretion takes place into cavities from which much re-absorption may occur are represented by the arteries to the intestine and the stomach.

The absorption of drugs from the stomach and intestines may be considerably retarded, and their action diminished, by the liver. Before reaching the general circulation, drugs absorbed from the intestinal canal must all pass through the liver (Fig. 5). In their passage they may be partly arrested and excreted again into the intestine along with the bile. They may be also partially destroyed. A larger quantity of a drug may thus be necessary to produce similar effects when introduced by the stomach than when injected directly into the circulation or under the skin—(1) because it may be absorbed more slowly by the vessels of the gastric or intestinal mucous membrane; (2) because a part of it may be arrested in the liver and excreted into the intestine along with the bile; (3) because a part of it may be actually destroyed in the liver.

The more rapid the absorption, or the slower the excretion, of any drug, the greater will be its effect. Thus the effect produced by the same dose of a medicine will be in proportion to the rapidity of its absorption from the different parts to which it has been applied, unless the differences be so slight that there has not been time for the excretion of any considerable quantity from the blood during the process. On this account we must diminish the dose of a medicine in order to obtain the same effect, according to the rapidity of absorption from the place to which we apply it. Absorption is quickest from serous membranes, next from intercellular tissue, and slowest from mucous

membranes. The vascularity and rate of absorption from intercellular tissue is greater on the temples, breast, and inner side

FIG. 6.—Diagram to illustrate the differences produced in the amount of a drug present in the organism by alterations in the rate of absorption and excretion. The lower funnel represents the organism. A represents the condition when a drug is rapidly introduced, as by injection into a vein. In this case the drug, *e.g.* curare, comes to be present in large quantities in the organism, and produces its full physiological effect. This is represented by the fulness of the lower funnel. And it does this notwithstanding the rapidity of excretion, which causes the drug to be quickly eliminated and to appear copiously in the urine, as represented by the fulness of the beaker into which the fluid flows from the lower funnel. B represents the condition when a drug is slowly absorbed and rapidly excreted, as when curare is given by the stomach. In this case the quantity present in the blood at any one time is very minute, as represented by the empty condition of the lower funnel. C represents the condition when absorption is rather quicker than excretion, as when a dose of morphine is given by the stomach. D represents the condition where absorption is moderate but excretion is interfered with, leading to accumulation in the blood, as where an active drug is given by the mouth and the kidneys are much degenerated.

of the arms and legs than on their outer surfaces, or on the back.[1] It should not be forgotten that any drug introduced into the stomach, but not absorbed into the blood, is as much outside the body as if it were in the hand, for any effect it will have on

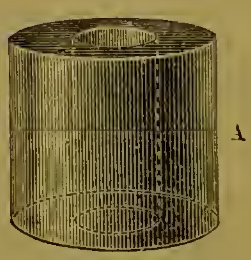

FIG. 7.—Diagrammatic representation of the body. A is a box to represent the tissues. B is an inner tube to represent the intestinal canal. It is obvious that anything which is merely in the inner tube is outside the box, and, similarly, anything which is merely in the intestinal canal is outside the body.

the system, provided always it have no local action on the gastric walls. But if it act directly on the walls of the stomach, it may have an effect which it would not have when held in the hand

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[1] Eulenburg, *Hypodermatische Injection der Arzneimittel*, 3rd edit. p. 65.

or applied to the skin. Thus mustard, which would produce redness and burning of the skin, will cause vomiting when swallowed; but opium, which does not act on the stomach itself, except by diminishing its sensibility, produces no apparent effect until after it has been absorbed.

By the difference between absorption and excretion under different circumstances or in different individuals,[1] the cumulative action of drugs, the effect of idiosyncrasy, habit, climate, condition of body, as fasting, &c., disease, and form of administration, can, to a certain extent, though not entirely, be explained; but experiments on some of these points are deficient, and the explanations now given are to some extent theoretical.

Duration of Action of Drugs.—When a soluble drug is introduced into the stomach, it will undergo absorption, and the whole of it may possibly be absorbed without any portion of it even passing into the intestine. After absorption into the blood it will either remain in the plasma or form a compound with the corpuscles. It will thus be carried to the liver, where part of it may be retained (*vide* p. 39). Such portions as pass through the liver will then be carried to the right side of the heart, to the pulmonary circulation, and then, passing to the left side of the heart, will be distributed to all parts of the body. As absorption continues, the quantity of the drug in the stomach will gradually diminish, while that in the circulation will increase to a certain extent; this extent, however, will depend upon the activity of the eliminating organs. The drug will be carried to all parts of the body, both to the eliminating organs and to those connected with the other functions of the organism. It will enter into combination, more or less firm, with all those organs which have any attraction for it, and will more or less modify their functional activity. In the processes of tissue-change, which are constantly going on, the combination between the drug and the organs will be gradually destroyed; and, being again returned to the circulation, it will undergo gradual elimination. The method in which elimination occurs will also depend, to a certain extent, on the selective action of the eliminating organs; thus soluble substances are usually eliminated most readily by the kidneys, while salts of the heavy metals, which form insoluble compounds with albumen, are eliminated to a great extent by mucous membranes.

Cumulative Action.—If a substance be naturally so slowly excreted from the body that the whole of the dose in ordinary use is not excreted before another is given, the amount present in the body will gradually increase, just like the curare in Hermann's experiment, and will produce an increasing or cumulative effect. Examples of this are to be found in metallic preparations,

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[1] Children absorb more quickly than adults, so opium is more dangerous to them. Marx, *Lehre von den Giften*, vol. ii. p. 117.

such as those of mercury or lead, which are excreted very slowly; or in some of the organic alkaloids, if given in sufficiently large and frequent doses. The sparingly soluble alkaloids which form stable compounds with the tissues and are thus slowly eliminated are more liable to prove cumulative. The size of the dose and the frequency with which it must be repeated in order to produce a cumulative effect will differ according to the rapidity with which the drug is excreted; for, if excretion be rapid, a larger dose or more frequent repetition will be required.

Sometimes the symptoms of the physiological action of a drug instead of increasing gradually may do so suddenly, and it is to this kind of action that the term cumulative action is most usually applied. This may sometimes be due to a sparingly soluble drug accumulating in the intestinal canal, and being suddenly dissolved and absorbed on account of some change occurring in the intestinal contents; at other times it may be due to arrest of excretion, as in the case of the two vegetable active principles, digitalin and strychnine, to which an especial cumulative action is ascribed. After moderate doses of these drugs have been taken for some time, it is found that instead of the effects they produce increasing gradually, as we would expect from a gradual accumulation in the blood, the symptoms of poisoning become suddenly developed, in somewhat the same way as if the dose had been suddenly increased. It is evident that a diminution in the quantity excreted will produce this effect as readily as an increase in the quantity taken, and this is probably the true cause of the phenomenon. When digitalin has been taken for some time and accumulated to a certain extent in the blood, it causes a diminution in the amount of urine excreted, and this diminution is either accompanied or quickly followed by the other symptoms of poisoning.[1] The effect, indeed, seems exactly the same as Hermann would have obtained in his experiment if he had only partially compressed the renal arteries instead of ligaturing them completely. For digitalin appears to diminish the secretion of urine by causing a powerful contraction of the renal vessels,[2] and in large doses may completely arrest the secretion of urine,[3] and probably also the circulation through the kidneys. Strychnine has a similar action on the vessels.[4]

Effect of different Preparations.—When a drug is given in a soluble form, and in small bulk, it is more quickly absorbed and will have greater effect than when given in a less soluble

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[1] Brunton, *On Digitalis*, p. 39.
[2] Brunton and Power, *Proceedings of Royal Soc.*, 1874, No. 153, and *Centralblatt f. d. Med. Wiss.*, 1874, p. 497.
[3] Christison, *Edin. Med. Journ.*, vii. 149.
[4] Grützner, *Pflüger's Archiv*, 1876, Bd. xi. p. 601. Gärtner, *Separat-Abdruck a. d.* lxxx. *Bd. d. k. Akad. d. Wiss.* III. Abt., Dec. Heft, Jahrg. 1879.

form or much diluted. Thus drugs given in solution as tinctures will act, as a rule, more quickly than when given in the form of pill or powder.

Effect of Fasting.—When a drug is given upon an empty stomach, it is usually absorbed much more rapidly. Thus the same quantity of alcohol which would have no effect on a man if taken during or after dinner, might intoxicate him if taken on an empty stomach, and especially if he were thirsty, so that absorption occurred rapidly. Curare, although it is usually inert when placed in the stomach, is sometimes absorbed so rapidly from an empty stomach as to produce a certain amount of paralysis.

Besides the alterations in absorption we have to consider also the local action on the stomach itself, and the reflex effects which may be produced through the gastric nerves on other organs. Thus where we give a drug for its local action on the stomach itself, it is administered with the greatest effect during fasting, as it will come in contact with all parts of the gastric mucous membrane. An example of this is the use of a small dose of arsenic for gastric neuralgia or lientery.

But when we wish to prevent local action on the stomach—as, for example, when we give arsenic for its general effect on the system, in cases of skin-disease—we administer it after meals, so that it may be diluted by the food, and not irritate the stomach too much.

Effect of Conditions of the Stomach.—In some conditions of the nervous system, absorption takes place much more slowly than others; indeed, both digestion and absorption appear to be sometimes totally arrested. Thus in persons in whom a sick headache comes on some time after a meal the contents of the stomach are vomited after a while and the food is found to have undergone digestion but not absorption. If the meal be taken after the headache has come on it will be found, in some persons at least, that the food is vomited almost unchanged, both digestion and absorption appearing to be arrested. This condition exists also in delirium tremens, and in a case of this disease I have seen pieces of food thrown up in an undigested condition although they have been swallowed, as the patient has informed me, three or four days before. It is probable that in these conditions drugs are also not absorbed, and I think it is not improbable that the harmlessness of large doses of digitalis given in cases of delirium tremens is due to the non-absorption of the drug.

Effect of Habit.—The tissues seem to have a certain power of adapting themselves to changes in their surroundings. Thus salt-water amœbæ will die when placed at once in fresh water, but if the fresh water be added very gradually, they may by-and-by become accustomed to live in it. Fresh-water amœbæ also

have the power of becoming gradually accustomed to increasing quantities of salt gradually added to the water in which they live, and which would at once kill them if added suddenly. A similar power seems to be possessed by the tissues of the higher animals, in regard to some drugs at least. Thus the arsenic-eaters of Styria are able to consume—not only without injury, but with apparent benefit to themselves—a quantity of arsenic which would prove fatal to one unaccustomed to it. The same is the case with opium and morphine. With these latter drugs there seems to be hardly any limit to the quantity which can be taken after the habit has been once established, and after a certain dose has been exceeded.

It is possible, however, that in addition to a process of accommodation going on in the tissues, there is a slower absorption, and perhaps more rapid excretion, going on at the same time; for it is observed in the case of opium that sometimes the effect is not only diminished, but the time which elapses before it occurs is lengthened when persons have become accustomed to the drug.

In regard to the possibility of very slow absorption we must remember the power of the liver to arrest and excrete or to destroy poisons, especially as it is chiefly in the case of vegetable poisons that their power is lessened by habit, which has much less influence on the effect of inorganic substances. The **tolerance** of some inorganic drugs, and especially of tartar emetic in disease or after repeated doses, may be due to fever or the drug itself lessening the acidity of the stomach, and consequently the action of the drug, which acts most strongly in presence of an acid.

The Effect of Temperature.—Chemical reactions, as a rule, go on more rapidly the higher the temperature, excepting when very high temperatures are reached and dissociation occurs. The effect of drugs upon living organisms may be regarded as being to a great extent due to chemical union between the drugs and the organism, and therefore we should expect that alterations in temperature would greatly affect the action of drugs and that, as a rule, we should find that they would act with greater quickness when the temperature is high unless some other factor should be brought into operation by the increasing temperature. Experience confirms this expectation, and, as a matter of fact, the effect of temperature on the action of drugs is very great. At different temperatures the administration of the same drug may be followed by different results, and it is probable that a great number of the **contradictory observations** which we find in works on Pharmacology are due to this most important factor having been neglected in making the experiments. It is of the greatest importance to the physician also, as many of the cases of disease which he has to treat are accompanied by a rise in

temperature which may have a very important effect upon the action of the drugs which he administers.

The alteration produced in the effect of drugs by warmth, was first noticed by Alexander von Humboldt, who observed that warmth not only acted as a stimulant to the heart in increasing the power and rapidity of its contractions, but noticed that warmth increased the rapidity with which alcohol destroyed the irritability of a nerve, and potassium sulphide that of a muscle. Bernard observes generally that poisons act slightly on frogs when cooled down, and become more active the higher the temperature. The effect of warmth in stimulating the movements of protoplasmic structures, such as amœbæ and cilia, was investigated by Kühne; and, in an important research, Luchsinger experimented on the influence of warmth on the action of poisons on many organs, and found that the ciliary motion in the pharynx of the frog became paralysed by chloral, potassium carbonate, and tartrate of copper and sodium more and more quickly in proportion to the rise in temperature. On cooling down the ciliary movement again returned.

Dr. Cash and I have found that the action of veratrine or barium on muscle is very much altered by heat and cold. At ordinary temperatures contraction is greatly prolonged, but under the influence of either great heat or great cold the contraction again becomes nearly or quite normal.

Many, if not all, muscular poisons act more quickly with increased temperature; and frogs poisoned with chloral, copper, manganese, potash, and zinc are paralysed more quickly when the temperature is high, than when it is low, whether the alterations be produced artificially, or be due to differences in the season at which the experiments are made.

Rabbits poisoned with copper or potash also die more quickly when placed in a warm chamber than when left at the ordinary temperature.

The terminations of motor nerves in the muscles are also greatly affected by temperature.

Guanidine produces in the frog fibrillary twitchings of the muscles, which persist even in excised muscles, but are removed by curare, and are therefore in all probability dependent on an affection of the terminal ends of the motor nerves in the muscle. Luchsinger found that when four frogs are poisoned in this way, and one is placed in ice-water, another in water at 18°, a third at 25°, and a fourth at 32°, the fibrillary twitchings soon disappear from the muscles of the frog at 0°, and only return when its temperature is raised to about 18°. In the one at 18° convulsions occur, which are still greater in the one at 25°. In the frog at 32°, on the other hand, no abnormal appearance is to be remarked, and five times the dose may be given without doing it any harm.

This poison then resembles veratrine in acting only at ordinary temperatures, and in its action being abolished by excess of heat or cold.

The effect of temperature on **secreting nerves** is well marked. When the sciatic is stimulated in an animal, the corresponding foot usually begins to sweat, but the sweating is very much less if the foot is cooled down than if it is warm. A similar action is exerted by temperature upon the sweating produced by pilocarpine—a drug which appears to act by stimulating the ends of the secreting nerves. When the animal is cooled, this drug is much less powerful than when it is warm.

Overheating appears to have an opposite action, and when the foot is heated up to a certain temperature it does not secrete nearly so readily, even though the glands themselves are not injured, and secretion may commence after the lapse of a little time.

The influence of poisons on the **heart** of the frog is also modified by temperature. Kronecker found that its beats were arrested by ether easily and quickly when the temperature was high, but with great difficulty when it was low. Ringer found that a small dose of veratrine greatly affects the ventricle at a moderate or high temperature, but at a low temperature produces no effect.[1]

Luchsinger noticed that when the frog's heart had been arrested by passing dilute solutions of chloral, copper, or potassium carbonate through at 25° C., the pulsations again began when the temperature was reduced to 15° C. When, on the contrary, the heart had been arrested in a similar manner, at a temperature of 5° C., pulsations could then be induced by warming it to 15°.

Some extraordinary observations on the effect of temperature upon the action of drugs on the **spinal cord** have been made by Kunde and Foster, who have found that, in a number of frogs poisoned with strychnine and exposed to different temperatures, raising the temperature diminishes the convulsions, while cold increases them if small doses are employed. Raising the temperature, indeed, may not only diminish but entirely abolish the convulsions, while putting a frog in ice may bring them on when they would not otherwise appear, and cause them to last for no less than twenty-four hours. When large doses are employed the opposite effect is produced; raising the temperature then increases the convulsions, while cooling the frog down to 0° abolishes them.

An observation similar in some respects, though differing in others, has been made on the effect of temperature on the action of picrotoxin by Luchsinger.[2] When this poison is given to three

[1] Ringer, *Archives of Medicine*, vol. vii. Feb. 1882, p. 5.
[2] Luchsinger, *Physiologische Studien*, Leipzig, 1882.

frogs, and they are then placed in water at 0°, 15°, and 32°, in a few minutes the convulsions occur in the one at 32°, shortly afterwards in that at 15°, while the one at 0° remains for a long time completely unaffected, and only exhibits signs of convulsion when the dose has been very great indeed, or when it is taken out of the cold bath.

The effect of warmth in **accelerating death** from muscular poisons has already been mentioned.

The power of warmth to **preserve life** in narcotic poisoning was observed by Hermann in relation to alcohol, which rabbits bear better when they are somewhat warmed.[1] Its extraordinary effect in preventing death in animals poisoned with chloral was noticed by Stricker, and more thoroughly worked out by myself at his suggestion.[2] Death by chloral appeared from my experiments to be in a great measure due to continued loss of heat from the animal. This seems to be the case also in metallic poisoning by copper, manganese, mercury, platinum, potassium, thallium, tungsten, and zinc. Its cause appears to be twofold: (1) the poisons lessen combustion in the body, and the amount of heat produced, as is shown by their diminishing the amount of carbonic acid excreted; (2) besides disturbing the production they also disturb the regulation of heat, so that animals poisoned by them have less power of resisting the influence of external temperature, and therefore the temperature rises more quickly when they are put in a warm chamber, as well as sinks more quickly when they are exposed to cold.

All these observations show that the **definition** of the **action of a drug**, already given (p. 5), must be still further modified, and we must define it as the reaction between the drug and the various parts of the body **at a certain temperature.**

Thomas[3] found that digitalis has sometimes no action on the pulse in pneumonia. As the slowing of the pulse produced by this drug is to some extent effected through the vagi, it occurred to me that its want of action in this disease might be due to the paralysis of these nerves by heat. On testing the action of heat, however, on the vagus, in rabbits deeply chloralised, I found that it was not paralysed at a temperature just sufficient to kill the animal.[4] Cash and I, however, have found that though the peripheral ends of the vagi are not completely paralysed by high temperature, the roots of the vagus in the medulla appear to be so, and probably the want of action of digitalis, when the temperature is high, is due to this paralysis (*vide* Digitalis).

The abnormal effect which opium has in some cases of fever —causing excitement instead of sleep—is occasionally most

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[1] Hermann, *Arch. f. Anat. u. Physiol.* 1867, p. 64.
[2] Lauder Brunton, *Journal of Anatomy and Physiology*, vol. viii.
[3] *Arch. f. Heilk.*, vol. iv. 329, 1865.
[4] *St. Bartholomew's Hospital Reports*, 1871, p. 216.

distressing to the physician. It is possible that this may be partly due to the temperature, and that the combination of tartar emetic with the opium may owe some of its utility to its effect in lowering temperature, although not improbably both it and another useful combination with chloral also act more perfectly on account of the depressing action on the circulation. These are points, however, on which further observations are greatly needed.

Climate.—It is said that the action of narcotic drugs is greater in warm climates than in cold, and that smaller doses are therefore required to produce a similar effect. If this statement be true, it may be due to the higher temperature, for Crombie has shown that in India the average temperature of the body is about half a degree higher than in England. It may, however, be due to the slower elimination of the drug by the urine; because in hot climates the secretion of the skin is apt to be much greater, and the secretion of urine and elimination by it consequently less.

Time of Day.—In healthy persons fluctuations of the body-temperature occur. The lowest temperatures occur at night between 10 P.M. and 1 A.M., and in the early morning between 6 and 8 A.M. The highest temperature occurs between 4 and 5 in the afternoon.

The action of drugs may be partially altered by the slight variations in temperature which occur within the body, and perhaps still more by the variations in tissue-change, of which these fluctuations of temperature are the indication. Thus the necessity for great attention to the administration of stimulants in the early hours of the morning in cases of threatening collapse has long been recognised.

Effect of Season.—The action of drugs is altered by the changes in temperature due to the seasons. Galen supposed that the quantity of blood in the body was increased in spring, and in this country, till within recent years, it was a common custom for people to be regularly bled every spring. Purgatives were not unfrequently administered also at the same time. There are, no doubt, changes corresponding with the seasons in the human organisation, although these are better marked in the lower animals; *e.g.* deer, in which the antlers bud regularly in spring and reach perfection just at the breeding season. It is possible that the abolition of the practice of bleeding in spring and the changes in other plans of treatment formerly adopted, may not be altogether due, as some suppose, to increased knowledge on our part, but rather to the occurrence of **a change of type** not only in diseases but also in slight ailments, and to the need for such treatment having disappeared. Formerly, before the introduction of coaches, and still more of railways, locomotion was difficult and transportation was expensive; in consequence

of this, the food consumed by the generality of people was different in character, loaf bread being very little used, and salt meat often used for weeks and months together during the winter, with comparatively few vegetables. Such a diet might naturally lead to a condition of body which would be benefited by bleeding and purgatives.

Effect of Disease.—The direct and indirect, the local and remote action of drugs upon the complicated mechanism of a mammalian body is so perplexing that the attempt to ascertain the precise mode of action of a drug by its mere administration, either to a healthy man or to healthy animals, and observation of its effect upon them, is hopeless.

Moreover, the object that we really wish to attain is the power to relieve human suffering, and to avert the premature death due to disease. But in disease we have new factors; changes are produced by it in the functions of the body, and the reaction of the diseased organism to the drugs which we administer is oftentimes different from that of a healthy one. To a man suffering from cholera, for example, enormous doses of drugs have been given without the least effect; and, in the wakefulness of fever, the opium which ought to produce sleep may simply cause excitement and delirium.

Use of Experiments.

As we have seen, the problems put before us are too complicated to be solved directly, and we must therefore simplify them.

This is done in four ways:—

1st, by observation of the effects of drugs on animals with a **simpler organism** than our own, such as amœbæ or frogs;

2ndly, by **applying** the drug to some **part** of an animal body more or less completely **separated** from the rest, such as, for example, the muscle and nerve, or the heart of a frog separated from the body; and

3rdly, by **preventing** the drug from **reaching one part** of the body while it acts on the others, as by ligaturing an artery, as in Bernard's or Kölliker's experiments on curare.

4thly, by producing artificial **changes** in the **relations** of the various parts of the body of higher animals, either before or after administration of a drug, as, for example, by dividing the vagi, in order to ascertain how far the change produced in the beats of the heart by a drug is due to its action upon it through these nerves.

Comparative Pharmacology.—It may seem almost absurd to those unacquainted with the subject, that so much attention should be devoted to experiments on the effect of drugs on the lower animals, when our object is, as we have just stated, to ascertain their action upon human beings, and their mode of employment in the diseases of man.

But in the study of Pharmacology, just as in Histology, very much is to be learned by comparative studies. In his lectures, Ranvier admirably defines General Anatomy as Comparative Histology limited to a single organism. He illustrates this by showing that the different modes of movement which occur in some of the lower classes of the animal kingdom are to be found united in the highest. Thus leucocytes of the blood move about like amœbæ. The epithelium of the respiratory passages is provided, like infusoria, with cilia; and while some muscles have the power of rapid contraction, others contract slowly, like those of some invertebrata.[1]

We have thus in certain parts of the bodies of the higher animals and of man, anatomical elements whose functions are performed in a way resembling that of organisms low in the scale of existence, and by examining the effects of drugs upon these low organisms we acquire knowledge which aids us in determining the action of drugs upon similar anatomical elements in the human body.

In his admirable lecture on Elemental Pathology, Sir James Paget draws attention to the distinction between the conditions of life and the essential properties of living things; and to the fact that, while the various parts of a complicated organism like the human body are closely connected together, and made to work in harmony for the common good of the organism in health, yet each part retains its own mode of life, and may sometimes develop to an excessive extent at the expense of the rest, and may destroy the organism, and itself as well. We see the power which each part possesses of carrying on individual life apart from the rest best in lower organisms or in inorganic substances, where the parts are less dependent on the welfare of the whole.

Thus, in crystals, a chip which has been broken off is replaced, and the form of the crystal restored, by putting it in a solution which will yield it the proper kind of material required. When a hydra is cut in two, each part grows into a perfect individual: a tail growing to the head part, and a head growing to the tail part. When a claw has been broken off a crab or lobster, a new one will by-and-by grow; but if the animal be divided in two, unlike the hydra it will die.

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[1] *Leçons d'anatomie générale sur le système musculaire*, par L. Ranvier. Paris, 1880, p. 46.

As we ascend in the scale of existence the power of repair becomes less perfect. But even in the human being we see that the different parts retain their individual life, and if put into proper conditions may live, although the original body from which they were obtained were to die. Teeth, for example, which have been extracted from one person have been transplanted and grown in the jaws of another; and the transplantation of hair, skin, or of periosteum is perfectly practicable.

Idiosyncrasy.—In their onward development from the lowest forms of life, man and the higher animals have not only permanently retained in their bodies certain parts which resemble organisms low in the scale of existence, but every now and again a tendency to reversion appears in certain individuals, and we thus get anatomical abnormalities and malformations.

These were formerly inexplicable, but the doctrine of evolution has thrown much light on their probable causation.

Now and again we also meet with peculiarities in the reaction between drugs and parts of the human body in certain individuals.

Some persons, for example, are like pigeons—only slightly affected by opium—and can take enormous doses of it without any apparent effect. Others, again, are peculiarly sensitive to the action of certain medicines, and a dose of a mercurial preparation, which would have but a slight purgative action on one, will produce intense salivation in another.

These personal peculiarities in regard to the action of drugs, or idiosyncrasies, as they are termed, have been, and are still, very perplexing to the medical practitioner. It is probable, however, that a more complete study of comparative pharmacology will enable us, to some extent at least, to recognise these, and thus to avoid the inconvenience which they occasion.

Experiments upon Healthy Man.—As the action of drugs upon animals is to a certain extent different from that on man, it is undoubtedly desirable to ascertain the action of drugs by experiments upon healthy man. This is all the more necessary because by experiments upon animals we are able to discover only the ruder differences between drugs, and we cannot ascertain the finer shades of action, both because it is in man alone that these finer differences occur, and because it is he alone who can give information regarding slight changes which he can perceive in his own organism, but which are imperceptible to others who may be observing him. There is no doubt that many observers of this sort, several of whom have been homœopathists, have done good service to medicine by carefully noting and carefully comparing the symptoms produced by various drugs. These observations, however, are liable to fallacies, as I will presently mention.

Fallacies of Experiment upon Man.—But the high development of the nervous system in man, its susceptibility to various influences, and the power of expression which man possesses—the very qualities which render him such a valuable subject for experiment make experiments upon him all the more liable to fallacy. Thus we find that in the experiments of Heinrich and Dworzak aconite was found to cause neuralgic pains in the face; but unfortunately these observers have not mentioned whether any carious teeth were present, and so we cannot ascertain whether the neuralgia was due to the action of the aconite itself upon healthy nerves, or to alterations in the circulation of the alveoli lodging decayed teeth.

One of the most marked examples of the fallacies occurring in experiments upon man, and of the errors to which such fallacies may lead, is to be found in the provings which Hahnemann made of cinchona bark, and which led him to formulate the doctrine of homœopathy. Hahnemann, who had suffered from ague,[1] for the sake of experiment, took for several days 4 drachms of good cinchona bark twice a day, and then began to suffer from all the ordinary symptoms of intermittent fever. On leaving off the drug he soon became quite well. He therefore concluded that cinchona bark, which was well known to be a remedy for ague, could also produce it.

Everyone who has an extended experience of ague knows well that even when patients have been free from any symptoms of the disease for a considerable length of time, they may be caused to reappear by various conditions, and more especially by anything that irritates the stomach or intestines. I have not myself seen a case of ague brought on by the administration of cinchona bark, but I have seen it occur after a succession of heavy dinners in a patient who had been long free from it. Powdered cinchona is certainly irritant, and Jörg found that in two-drachm doses it might cause flatulence, irritation, and nausea. Hahnemann took it in double this dose, and in all probability the ague which it brought on was simply due to gastric irritation, and not to any specific action of the cinchona. Had Hahnemann taken any other irritant which disagreed with him—say tartar emetic, or perhaps even pork-pie—he might have suffered in the same way, and yet pork-pie could hardly be said to be a specific for ague.

Experiments in Disease.—In the present state of medicine every attempt which we make to treat disease by the administration of medicine partakes more or less of the nature of experiment, because we can rarely be absolutely certain that the drug

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[1] *History of Homœopathy.* By Wilhelm Amcke, M.D. Translated by Alfred E. Drysdale, M.B. Edited by R. E. Dudgeon, M.D. London. Published for the British Homœopathic Society, by E. Gould & Son, 59 Moorgate Street. 1885

will have precisely the effect which we desire. As the phrase is, 'We try one medicine, and then we try another.' If human life were not so valuable, we might pursue a series of systematic experiments, and gain valuable information; but it is impossible for a physician to treat the patient who calls upon him for aid in any other way than that which seems likely to be the best for the patient's welfare. Here again the homœopathists have done good service, because by administering to the patient medicines in which they believed, but which could neither do good nor harm, they have taught us the natural course of some diseases, which we could not otherwise have learned.

Objections to Experiment.—Some people object entirely to experiments upon animals. They do this chiefly on two grounds. The first is that such experiments are useless, and the second is that, even if they were useful, we have no right to inflict pain upon animals.

The first objection is due to ignorance. Almost all our exact knowledge of the action of drugs on the various organs of the body, as well as the physiological functions of these organisms themselves, has been obtained by experiments on animals.

The second objection is one which, if pushed to its utmost limits and steadily carried out, would soon drive man off the face of the earth.

The struggle for existence is constantly going on, not only between man and man, but between man, the lower animals and plants, and man's very being depends upon his success.

We kill animals for food. We destroy them when they are dangerous like the tiger or cobra, or destructive like the rat or mouse. We oblige them to work for us, for no reward but their food; and we urge them on by whip and spur when they are unwilling or flag. No one would think of blaming the messenger who should apply whip and spur to bring a reprieve, and thus save the life of a human being about to die on the scaffold, even although his horse should die under him at the end of the journey. Humane people will give an extra shilling to a cab-man in order that they may catch the train which will take them to soothe the dying moments of a friend, without regarding the consequences to the cab-horse. Yet if one-tenth of the suffering which the horse has to endure in either of the cases just mentioned were to be inflicted by a physiologist in order to obtain the knowledge which would help to relieve the suffering and lengthen the life, not of one human being only, but of thousands, many persons would exclaim against him. Such objections as these are due either to want of knowledge or want of thought on the part of the people who make them. They either do not know the benefits which medicine derives from experiment, or they thoughtlessly (sometimes, perhaps, wilfully) ignore the evidence regarding the utility of experiment.

One of the most important objections that has been raised to this mode of experiment is that the action of drugs on the lower animals is quite different from their action on man. This objection has a certain amount of truth, but is in the main groundless. The action of drugs on man differs from that on the lower animals chiefly in respect to the brain, which is so much more greatly developed in man.

Where the structure of an organ or tissue is nearly the same in man and in the lower animals, the action of drugs upon it is similar. Thus we find that carbonic oxide and nitrites produce similar changes in the blood of frogs, dogs, and man, that curâre paralyses the motor nerves alike in them all, and veratrine exerts upon the muscles of each its peculiar stimulant and paralysing action.

Where differences exist in the structure of the various organs, we find, as we would naturally expect, differences in their reaction to drugs. Thus the heart of the frog is simpler than that of dogs or men, and less affected by the central nervous system. We consequently find that while such a drug as digitalis has a somewhat similar action upon the hearts of frogs, dogs, and men, there are certain differences between its effect upon the heart of a frog and that of mammals. In all it seems to affect the muscular substance and cause increased contraction. But while the frog almost invariably dies with the heart in a state of tetanic contraction, this is not the case with dogs or men, where the heart sometimes is found in diastole after death.

Ipecacuanha or tartar emetic will cause vomiting in man, but does not do so in rabbits. The reason of this is that the position of the stomach in the rabbit is different from that in man, and is such that the animal cannot vomit. In dogs, however, the position of the stomach agrees with that of man, and tartar emetic or ipecacuanha causes vomiting in both. Belladonna offers another example of apparent difference in action—a considerable dose of belladonna will produce almost no apparent effect upon a rabbit, while a smaller dose in a dog or a man would cause the rapidity of the pulse to be nearly doubled. Yet in all three—rabbits, dogs, and men—belladonna paralyses the power of the vagus over the heart. The difference is, that in rabbits the vagus normally exerts but little action on the heart, and the effect of its paralysis is consequently slight or hardly appreciable, the pulse being normally almost as quick as it is after the vagus is paralysed. In dogs and men, on the contrary, the vagus is constantly exerting considerable restraining power over the heart, and the effects of its paralysis at once attract attention.

An example of the apparent difference in the effect of a drug on different animals is afforded by nitrite of amyl. If we measure the pressure of the blood in the arteries of a rabbit and of a dog.

and then cause them to inhale nitrite of amyl, we find that the small vessels have become widened and allow the blood to pass easily out of the arterial system into the veins, so that the pressure sinks considerably in the rabbit, whereas it sinks only slightly in the dog. The action seems at first sight different; but when we examine it more closely, we find that the heart of the dog is no longer beating slowly, but very quickly, so as to keep up the pressure, notwithstanding the rapid flow of the blood through the widened vessels, while the heart of the rabbit was going so fast before that it could not go much more quickly. If we cut the vagi in the dog, so that the heart goes as quickly as in the rabbit before it begins to inhale, the blood-pressure sinks during the inhalation, just as it does in the rabbit.[1]

One of the most marked differences between the action of a drug upon lower animals and upon man is to be found in the effect of morphine upon frogs and upon pigeons. In frogs it causes convulsions; on pigeons, even in large doses, it produces no apparent effect. But although its effects are not appreciable to the eye, they exist nevertheless, and on applying the thermometer it is found that morphine lowers the temperature of pigeons many degrees. On comparing the effect of the drug on frogs with its effect on man, we see that in the frog the cerebral hemispheres are very slightly developed indeed as compared with man, and in the latter the effects of the drug upon the spinal cord are usually completely concealed by the narcotic effect of the drug upon the brain. In children, however, and in some races of man where the cerebral hemispheres are less developed than in Europeans, the convulsant action of morphine manifests itself. Occasionally we find individuals who are almost proof against the action of morphine, and who take large doses of it without any apparent effect. Whether in these persons it lowers the temperature as it does in pigeons is a point which remains to be ascertained.

By means of experiments upon animals, then, we are able to ascertain the action of drugs upon those organs of the body which are alike in man and animals; and the very differences which exist between the various sorts of animals, help us to understand the action of drugs more thoroughly.

Erroneous Deductions from Experiments.—A great fault —and one which is only too common in the works of experimental pharmacologists—is that of drawing **general conclusions** from **limited data.**

One experimenter tries the effect of a drug, let us say tartar emetic, upon rabbits. He finds that they do not vomit, and instead of drawing the only warrantable conclusion, viz. that tartar

[1] Lauder Brunton, 'Action of Nitrite of Amyl on the Circulation,' *Journal of Anatomy and Physiology*, vol. v. p. 95.

emetic does not cause vomiting in rabbits, he draws the general one—that tartar emetic does not cause vomiting in animals. Another tries it upon dogs, and he finds they all vomit. Instead of the limited conclusion that tartar emetic makes dogs vomit, he draws the general conclusion that it makes animals in general vomit. The two observers are equally positive in regard to their facts—each is assured that he himself is right, and that the other is totally wrong. The reason of the discrepancy is simply that the conditions under which the experiments have been performed were different, but the observers have not taken these differences into account when drawing their conclusions. A third observer then comes, perhaps, and by further experiments reconciles the apparently contradictory statements. Thus one experimenter tries the effect of caffeine upon frogs; he finds that it produces rigor mortis in the muscles. Another tries the same drug, and finds no such result. These two observations are completely contradictory, until a third tries the effect of the drug upon two species of frog, and finds that while the muscles of the *rana esculenta* are but slightly affected, those of the *rana temporaria* are rendered rigid.[1]

These apparent contradictions in the results of different observers are exceedingly puzzling to the student, but nothing is more instructive to those who are actually working at the subject.

The utility of apparent exceptions was fully recognised by Claude Bernard, who says: 'In physiological studies we must always carefully note any fact which does not accord with received ideas. It is always from the examination and the discussion of this exceptional fact that a discovery will be made, if there is one to make.'[2]

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[1] Schmiedeberg, *Arch. f. exper. Path. u. Pharmak.*, Bd. ii. p. 62.
[2] Bernard, *Liquides de l'organisme*, tom. i. p. 258.

CHAPTER III.

ACTION OF DRUGS ON PROTOPLASM, BLOOD, AND LOW ORGANISMS.

Action of Drugs on Albumin.

In all living bodies we find that the protoplasm is of a more or less albuminous nature.

Albuminous substances possess a very complex inter-molecular grouping, and very high atomic weights. Many different forms are found in animals, and along with albumins we must associate bodies like mucin, which probably have a very important relation to it, inasmuch as a body nearly, if not quite, identical with mucin forms the nucleus of the red blood-corpuscles in fowls,[1] and a substance of an allied nature also occurs in the circulating fluid which represents the blood in the echinodermata.[2] The albumin of serum may be taken as a representative of such substances; it is soluble in water, but, at a certain temperature, is **coagulated** and precipitated. It is coagulated also by alcohol, but if the coagulum is quickly placed in water it redissolves; if allowed to remain for some time exposed to the action of the alcohol it becomes permanent and insoluble. An insoluble precipitate also falls on the addition of tannic acid, both lead acetates, and mercuric chloride. The reagents just mentioned precipitate all the albumins, even from somewhat dilute solutions; in strong solutions precipitates are also formed by silver nitrate, copper sulphate, and zinc chloride.

When these are added to albumin containing only a small quantity of water, as, for example, the white of an egg, they form with it a solid mass of **albuminate**. A small quantity of strong potash added to the white of egg produces a solid transparent jelly of albuminate of potash, and a similar but opaque jelly is formed by the use of caustic lime or baryta in the place of potash: these albuminates are, however, soluble in water.

Albumin dissolves in alkalies, and may be partly precipitated by neutralising. The alkaline solution is not coagulated by heat, and, in fact, the substance present in the solution is no longer serum albumin, but a compound of the albumin with the alkali, or **alkali-albuminate**.

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[1] Lauder Brunton after Kühne, *Journ. of Anat. and Physiol.* Nov. 1869.

[2] Schäfer, *Proc. Roy. Soc.*, vol. xxxiv., p. 370.

Albumin is precipitated by a small quantity and dissolved by excess of most mineral acids, forming with them **acid-albuminates**; thus a watery solution of albumin is precipitated by concentrated nitric, sulphuric, or hydrochloric acid. It is also precipitated by acetic acid along with a considerable quantity of a neutral salt of an alkali or alkaline earth, or of gum arabic or dextrin. This precipitation is perhaps best marked with nitric acid, but it only occurs with moderate quantities of nitric acid. When a minute quantity only of the acid is added, no precipitation takes place, and the solution remains clear; but a nitric-acid-albuminate containing a small quantity of acid is formed, and if the solution is now boiled no coagulum will form. On the addition of more acid, however, a second nitric-acid-albuminate, insoluble in water, is produced, and a precipitate falls. On the addition of more acid still, the precipitate is redissolved, and a third nitric-acid-albuminate is formed, soluble in water, and not precipitated on boiling.

The temperature at which albumin coagulates is altered by acids and alkalies. Alkalies generally tend to raise the temperature of coagulation, and when added in large quantities prevent it altogether.

Very dilute acetic and phosphoric acid, on the other hand, tend to lower the coagulating point, although large quantities may interfere with coagulation.

Neutral salts, such as sodium chloride or sulphate, also lower the coagulating point.

The **organic alkaloids** which have such a powerful action on the animal body appear to resemble acids rather than alkalies in their effect upon albumin, because, according to Rossbach, they lower considerably instead of raising the point of coagulation.

Albumin undergoes an extraordinary change in consequence of the action of ozone, and becomes, after exposure to it, uncoagulable by boiling, and by acids, excepting in large quantities, and by metallic salts, with the exception of basic acetate of lead, and of alcohol.

The action of alkaloids upon this ozonised albumin is even more remarkable than upon ordinary albumin, for when mixed with it in small quantity, they restore its coagulability to the albumin, and cause it to coagulate far under the boiling-point. When added to the albumin before exposure to a stream of ozone, they prevent the albumin being altered by it, in the way which it would otherwise be, and it remains coagulable by heat, in the same way as if it had not been exposed to the action of ozone at all. It is therefore evident that the alkaloids not only increase the coagulability of ordinary albumin at a high temperature, but that they act upon it at ordinary temperatures (30°–40° C.) and destroy its affinity for ozone. This action will naturally interfere

with the processes of oxidation in protoplasm; but the methods of examining this action will be described later on (p. 69).

When a solution of pure albumin is added to a mixture of guaiac and vegetable protoplasm, it greatly lessens the blue colour, which would otherwise be produced. The cause of this appears to be that albumins or albuminous substances have such an affinity for ozone that they take it up instead of allowing it to act on the guaiac. This affinity for ozone is diminished by the action of alkaloids.

This is shown by taking several tubes containing an albuminous solution of a certain strength. Reserving one as a standard, the alkaloids are added to the others, and after a certain time has elapsed, so as to allow the alkaloid to affect the albumin, a small quantity of lettuce water is mixed with each, and then a little guaiac. In the standard one the colour will be least, because the albumin not having been acted upon by the alkaloids will interfere with the reaction of the lettuce water and the guaiac upon each other. In the others a blue colour will appear with greater or less intensity, according as the albumin has been more or less affected by the alkaloid. This experiment, however, is not free from fallacy, because there is to be considered not merely the action of the alkaloid upon the albumin, but its action on the protoplasm as well, and it is therefore advisable to use it in a quantity which is small as compared with the amount of albumin employed.[1]

Action of Drugs on Protoplasmic Movements.

The **amœba** consists of a small mass of structureless protoplasm, without any distinct cell-wall.

It contains numerous granules and nucleus, with nucleolus, as well as one or more vacuoles, which appear to be small spaces filled with fluid.

Some amœbæ live in salt water, others in fresh water; and, although it may be impossible with the microscope to detect any marked difference between them, they exhibit a great difference in their reactions to drugs—the salt-water amœbæ being only slightly affected by them, while fresh-water amœbæ are readily susceptible to their action.

The amœba is nourished by simply adhering to any particle of food, closing over it and digesting it, and afterwards opening and ejecting the residue.

This protoplasmic mass is almost constantly altering in shape, pushing out projections at one point, and drawing them in at another. By this means, also, it moves about from place to place.

Method of Experimentation on Amœbæ and Leucocytes.—In experimenting on amœbæ, take a drop of slimy sediment, such as is found in the tanks of hothouses, and place it on the covering-glass of a microscope; this may then either be put on an object-glass, and the excess of water removed by filter-paper, or, still better, it may be inverted over the opening of a Stricker's warm stage.

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[1] Rossbach, *Verhandl. d. phys. med. Ges. zu Würzburg*, N.F., Band iii. p. 346.

When it is simply laid on the object-glass, a solution of the drug is added by putting a drop across the edge of the covering-glass, and allowing it to be drawn gradually underneath by capillary attraction.

Gases are best applied by means of a Stricker's stage, which is also convenient for experiments on solutions.

In experimenting on **leucocytes** with the aid of this stage, a covering-glass is applied to the cut surface of a newt's tail, or to the surface of a drop of blood, so that a very minute quantity of blood adheres to it.

The drug to be tested is kept dissolved in a ·65–·75 per cent. solution of common salt (Na Cl). The salt solution of this strength is often called simply *normal* salt solution, and is used instead of water, because water itself has a very destructive action on those forms of protoplasm, which are usually nourished by saline solutions, like blood or serum.

A drop of the salt solution containing the drug is placed over the blood on the covering-glass, and inverted over the warm stage as already described. If the experiment is to continue long, a rim of oil should be drawn around the edge of the covering-glass with a camel-hair pencil, so as to prevent evaporation.

The advantage of using such a small quantity of blood is, first, that it mixes rapidly and perfectly with the solution; and secondly, that it does not dilute the solution of the drug, and we thus know the strength of the drug used.

If we used a large drop of blood, we should have to employ a solution of the drug twice the strength we desire, so that when a drop of equal size was added to the blood, the mixture would contain the proper proportion.

Amœbæ.—The **effect** of **heat** and **cold** upon the movements is very marked, cold rendering them slow, or arresting them altogether. Heat at first greatly quickens their movements, but when raised to 35° C. it causes them to fall into a state of tetanic contraction and assume a spherical form.

This state is one of heat-tetanus, and if the temperature be now reduced, the movements will again reappear.

At a temperature of 40° C. they also become spherical and motionless. But their movements do not return when the temperature is reduced; they are in a state of heat-rigor, the high temperature having coagulated the protoplasm.

Slight **electrical** shocks from a coil increase the rapidity of the protoplasmic movements; stronger ones cause tetanic contraction; and numerous or powerful ones produce coagulation.

Common **salt** in very small quantity (a drop of 1 per cent. solution slowly added) first quickens the protoplasmic movements and then causes sudden tetanic contraction, and the expulsion of any food they may contain at the moment, and sometimes even expulsion of the nucleus.

When **water** is added so as again to dilute the mixture the amœbæ resume their movements.

Both **acids** and **alkalies**, when very dilute, increase the protoplasmic movements and afterwards arrest them.

Hydrochloric acid has a more powerful action than a solution of potash of a similar strength. It causes the amœba to contract and form a ball with a sharp double contour. In it, twitching movements first occur, which expel any food present. It then becomes pale and lumpy, and breaks up.

Potash causes them to swell up and assume the form of large pale vesicles, which quickly burst.

A **constant current** of **electricity** causes contraction and imperfect tetanus; and, if powerful and long kept up, the positive pole produces in the amœbæ near it the same changes as dilute hydrochloric acid, and the negative pole the same changes as are produced by an alkali such as potash.

Oxygen appears to be necessary for their life; its removal by means of hydrogen deprives the amœbæ of their power of motion, and finally causes contraction and coagulation.

Carbonic acid alone has a similar action to removal of oxygen and produces this effect both in the presence and absence of oxygen, but takes a longer time to do so when oxygen is present.[1]

Leucocytes.—In their appearance and movements leucocytes strongly resemble amœbæ: they are affected in a similar manner by heat, electricity, and drugs. Their resistance to the action of drugs varies somewhat in different animals. Those obtained from the blood of the newt, for example, are more resistant than those of the guinea-pig, and those of the female newt more resistant than those of the male, to the action of quinine.[2] Heat and cold affect the movements of leucocytes in very much the same way as those of amœbæ.

The movements of leucocytes, like those of amœbæ, are of **two kinds**, viz. movements of the protoplasmic pseudopods, while the leucocyte remains *in situ*. The pseudopods in this instance are generally of a waxy look and knoblike form.

Secondly, movements of migration from place to place; these movements are accompanied, or accomplished, through the projection of numerous fine filaments.

Effect of Drugs.— Cinchona alkaloids—quinine, quinidine, cinchonine, and cinchonidine have a remarkable power of arresting these movements in the proportion of 1 in 1,500. They quickly stop the migratory movements of leucocytes from the newt, and in a much larger proportion will arrest the movements of the knoblike pseudopods.

No very marked difference is observed in the strength of the cinchona alkaloids, though quinine seems to be somewhat the most powerful.

Sulphate of beberine is almost as powerful as the cinchona alkaloids.

Strychnine is very much less powerful than any of the alkaloids mentioned.

Potassium picrate and æsculin have but little action.[3]

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[1] Kühne, *Protoplasma und Contractilität*, pp. 28–53.
[2] Geltowsky, *Practitioner*, vol. viii. pp. 325–330.
[3] Buchanan Baxter, *Practitioner*, vol. xi. p. 321.

Movements of Leucocytes in the Blood-vessels.—In the processes of **inflammation** leucocytes pass in great numbers through the walls of the capillaries.

The effect of quinine in arresting their movements, when mixed with them directly, naturally leads one to expect that it may arrest their migration from the capillaries, when injected into the blood, and this anticipation has been realised in the experiments of Professor Binz.

To observe this phenomenon the brain of a frog is to be destroyed, and a little curare injected under the skin, in order to abolish any spinal reflex movements. It is then laid on a piece of cork, such as that shown in Fig. 8, with a hole at one side, over which a piece of glass is fastened about

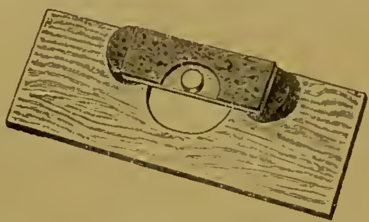

FIG. 8.—Apparatus for examining the mesentery of the frog under the microscope.

half an inch higher, by means of two other pieces of cork and some sealing-wax. On this a piece of sheet cork of the form shown in the figure, and a round piece of glass are cemented so as to form a channel, in which the intestine lies. The body of the frog is fixed to the cork, the abdomen opened, the intestines drawn out, and the mesentery fastened with very fine pins over the aperture. In half an hour, or two hours, the leucocytes pass rapidly through the walls of the capillaries, and afterwards wander through the tissues.

The drug may then be injected into the lymph-sac, or locally applied to the mesentery.

When quinine is applied locally to the mesentery in this condition it arrests the movements of the leucocytes, which have

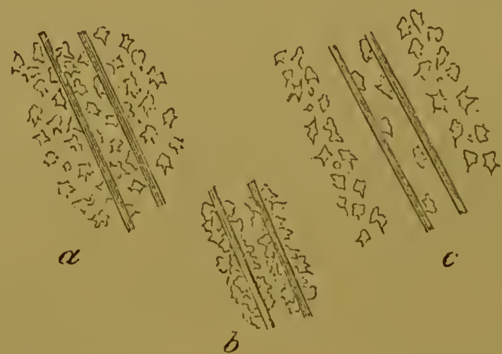

FIG. 9.—Diagram to illustrate the action of quinine on leucocytes, modified from Binz (*Das Wesen der Chininwirkung*. Berlin, 1868). The thick lines represent the walls of the blood-vessel, and numerous leucocytes are shown both inside it and outside distributed through the adjoining tissues. *a* represents the vessel before, and *b* after, the *local* application of quinine. The leucocytes outside the vessel have their movements arrested, and cannot wander on through the tissues, while those inside are not affected and continue to emigrate. *c* represents the effect of quinine injected into the circulation or lymph-sac. The leucocytes inside the vessel are here affected first, and their emigration stopped, while those outside still continue to travel onwards.

already emerged, but does not prevent those which are still within the vessels from going out; they therefore form a dense accumulation around the vessel (Fig. 9, *b*). When injected into

the circulation, on the contrary, the leucocytes which are in the vessels are prevented from passing from the capillaries, while those which have already passed out continue to wander onwards, and thus a clear space is left outside the vessel (Fig. 9, *c*).

The quantity of quinine necessary to produce this effect is $\frac{1}{25000}$th to $\frac{1}{20000}$th of the animal's weight.

If quinine were given to stop the exit of leucocytes from the vessels in peritonitis, three or four grammes would be required to be given within a short time, to a man weighing 150 lbs.

In guinea-pigs a dose of quinine sufficient to kill the animal does not stop the movements of the leucocytes in its blood, which are seen to go on, when a drop of it is examined after death.

Red Blood Corpuscles.—The size of the red corpuscles is diminished by carbonic acid, by morphine, or by warmth, either applied locally on the hot stage of a microscope, or acting on them in the vessels of an animal suffering from fever.

It is increased by oxygen, hydrocyanic acid, quinine, or cold; and an increase occurs also in cases of anæmia.[1]

The red corpuscles pass out of the capillaries like the white, but they do so very slowly indeed, and in small numbers, under ordinary circumstances. Excess of sodium chloride in the blood causes them to pass out much more quickly; [2] and rattle-snake poison, when locally applied, produces such sudden extravasation that it is impossible to follow the process: the whole field of the microscope becoming suddenly covered with blood.[3]

Action of Drugs on Infusoria.

Among the infusoria, like the amœbæ, each individual consists of a single mass of protoplasm, and not of a number of distinct cells; but the protoplasm is differentiated. Round the greater part of the animal it seems to be somewhat harder, so as to form a sort of skin, excepting at one place which is softer than the rest, serving for the ingress of food and the egress of egesta.

Instead of throwing out pseudopods, the body is either covered entirely with cilia or they are arranged round the mouth. Once it has entered by the mouth, the food finds its way all through the protoplasm of the body.

A contractile vesicle exists, which pulsates rhythmically.

Mode of Experimentation. — For the purpose of examining the action of drugs upon infusoria an infusion of hay is prepared some days previously. Two small pipettes are then made, which will deliver drops of equal size.

This is done by heating a piece of glass tubing in the middle, drawing it out, and cutting it across by a scratch with a triangular file (Fig. 10). With one of these a drop of hay-infusion is placed on the covering-glass, which is inverted on a Stricker's stage and examined. In order to ascertain

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[1] Manassein, *Ueber die Dimensionen der Blutkörperchen unter verschiedenen Einflüssen.* Tübingen, 1872.

[2] Prussak, *Wiener Akad. Sitzungsber.* lvi., 1876 (Abth. 2), p. 13.

[3] Brunton and Fayrer, *Proc. Roy. Soc.*, February 1875, p. 271.

the lethal strength of a drug, a drop of a solution of the poison of a definite strength is then mixed with it, and the infusoria are examined again after a certain time.

FIG. 10.—Diagram to show the way of making small pipettes.

If they continue moving, another experiment is made with a stronger solution; but if they have completely stopped, it is repeated with a weaker one until the solution is of such a strength that the movements become very slight and cease almost immediately after mixing, and cannot be restored by the addition of water. As the two drops of fluid were of equal size, the lethal strength of the solution is just one half of that which was last added. By repeating the experiments in exactly the same way with different drugs, their relative poisonous properties are ascertained.

Heat increases the rapidity both of the rhythmical contractions of the vesicle and of the ciliary motion and consequently of the movements from place to place of the infusoria. It seems as if the cilia were not equally affected by heat, those which produce a longitudinal movement appearing to be acted upon more quickly than those which cause a movement of rotation. Both kinds are first stimulated and then paralysed.

At temperatures between 25° and 30° C. the contractions of the vesicle are greatly quickened, and the animal moves with great rapidity in the longitudinal direction.

Between 30° and 35° its movements are still very rapid, but it seems to have lost the power of direction; all the cilia seem in full action, and the movements of the individual are determined simply by their anatomical arrangement.

Above 40° the cilia, which act longitudinally, appear to have stopped and the animal rotates, at first very rapidly, then slower and slower until all movements cease, and the protoplasm appears to become fluid; but when the heat is still further raised it coagulates.[1]

Cold lessens the quickness of the rhythmical contractions of the vesicle, of the ciliary motion and of the movements from place to place. Weak **electrical currents** first quicken the ciliary motion and cause movements of rotation, then swelling of the protoplasm, slower movements, and finally apparent solution of the protoplasm.

Moderate currents produce a tetanic contraction of the protoplasm and of the cilia, while the contractile vesicle is unaffected.

Strong currents cause liquefaction of the protoplasm.

Saline solutions appear rather, if we may say so, to alter the conditions under which the infusoria live than to affect the protoplasm itself. Strong solutions cause them to shrivel and

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[1] Rossbach, 'Die rhythmischen Bewegungserscheinungen der einfachsten Organismen,' *Verh. d. Würzburger physik. med. Gesellsch.* A.N.F., Bd. ii., Separat-Abdruck, S. 23. This work contains a number of exceedingly interesting and valuable observations on the subject.

then to swell up and become motionless. This effect appears to be due to the solution altering the quantity of water which the protoplasm contains.

Weaker saline solutions, on the contrary, quicken their movements, and, instead of causing them to shrivel, make them swell up at once. Chloride of sodium, chloride, bromide, and chlorate of potassium, as well as alum, all have this effect.

Acids in minute quantities cause contraction both of the body and of the vesicle. The ciliary motion is at first quickened and then retarded; the rate of contraction of the vesicle is at once diminished.

Moderate quantities cause coagulation of the protoplasm with swelling and liquefaction after death.

Strong acids at once destroy the protoplasm.

Alkalies in minute quantities cause swelling of the protoplasm, dilatation and slowness of the contractile vesicle.

Moderate quantities at once arrest the movements, cause liquefaction of the protoplasm, and destroy its differentiation, the contractile vesicles and vacuoles disappearing. They then cause swelling, and finally solution.

In large quantities they produce immediate liquefaction of the whole body.

Other drugs appear to affect the protoplasm itself, and arrest its movements without producing any apparent change in it.

The most active are chlorine, bromine, corrosive sublimate, iodine, permanganate of potassium, and creasote.

Quinine is much less powerful than these, though it is much more so than most other organic alkaloids. Strychnine has only one-fourth the power of quinine.

Cobra poison at first greatly quickens the movements of infusoria and then arrests them, causing just before death a contraction of the protoplasm, which then expands to its ordinary size.

Relations of Motion and Oxidation.

All animals, from the lowest to the highest, evidence their life by motion at one time or another; and the energy required for this motion is maintained by processes of combustion.

The materials for this combustion, viz. oxygen, and fuel of some sort, or food, are derived from the external medium in which the animal lives; and in order to enable these substances to be available for each part of the animal body, we must have some kind of respiration and circulation going on in it.

In unicellular organisms, consisting of a single mass of protoplasm, the oxygen is derived from the water in which they swim, and both it and the nutritive material derived from the digestion

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of enclosed masses are circulated through the protoplasm by contractile vacuoles.

In sponges, where the organism no longer consists of one but of several cells united into a community, some of these are furnished with cilia, in order to send a current containing oxygen and food to the other cells having a less favoured position.

In higher animals, where many cells are built up to form one organism, we find a circulatory and respiratory apparatus fully developed.

The medium in which unicellular organisms live is the water in which they swim. The medium in which the cells composing the main parts of the bodies of higher animals, such as man, live, is not the air which surrounds the body, but the intercellular fluid in which the cells themselves are bathed.

As Claude Bernard points out with his usual clearness, the cells of the human body and the lowest unicellular organisms alike live in a liquid medium. From the layer of fluid surrounding it, the cell takes up the oxygen and food which this layer can yield. The supply being exhausted, a unicellular organism can move on elsewhere, but the cells in higher animals, being fixed and unable to move, require fresh portions of oxygen and of nutritive fluid to be brought to them.

This is effected by the slow circulation of the lymph in which the cells themselves are bathed and by the supply to the lymph of oxygen and nutritive material from the blood.

The circulation of the lymph is aided in many lower organisms by the motion of cilia, and this is found persisting in some parts of the higher animals, *e.g.* the central canal of the spinal cord.

Between the blood and the lymph an interchange goes on, oxygen passing from the blood to the lymph or intercellular fluid, and carbonic acid from the lymph to the blood.

This interchange of gases between the blood, the intercellular fluid, and the cells is termed **internal respiration.**

In order to maintain this, a constant current of blood must take place; and when its circulation is locally arrested it becomes deprived of oxygen and loaded with carbonic acid, so that the cells in the district in which the stagnation occurs suffer from local asphyxia, while the other parts of the body may be perfectly healthy.

When the general circulation is arrested by stoppage of the heart, by obstruction of the pulmonary arteries, or by the rupture of an aneurism draining the blood away, the whole body suffers in a similar manner from general asphyxia by the cessation of internal respiration.

If oxygen were simply dissolved in the blood, the quantity which would be conveyed to the tissues would be too small for their wants, and we therefore have as an oxygen-carrier a sub-

stance capable of taking up a large quantity of oxygen, of readily forming a loose compound with it, and of again giving it off readily to oxidisable substances.

In man and mammals and many of the lower animals this substance is hæmoglobin containing iron. In some annelids it is a green substance, chlorocruorin; and in the octopus and some crustaceans it is a blue body, hæmocyanin, containing copper.[1]

In order to remove carbonic acid taken up from the tissues and obtain a fresh supply of oxygen, an interchange takes place between the blood and the external air in the lungs; this is **external respiration.** Without any direct influence being exerted upon the cells of the animal body themselves, they may be affected and their **nutrition** greatly **modified** by:

1st. Alterations in the circulation of the intercellular fluid or lymph in which they are bathed.

2nd. In the greater or less rapidity of circulation of blood locally.

3rd. In the circulation generally, from changes in the heart and blood-vessels generally.

4th. Changes in the oxygen-carrying power of the blood, either from alterations in its power to take up or give off oxygen.

5th. Changes in the external respiration.

All these conditions may be altered by drugs, or at least by therapeutic measures. Thus the circulation of lymph in a part may be increased by shampooing, and its accumulation in a case of dropsy may be removed by incision, by puncture, or by drainage.

The circulation of blood may be arrested locally and gangrene induced by the continuous use of ergot. It may be increased by the use of local stimulants or irritants.

The circulation generally may be affected by the large class of vascular stimulants and depressants, to be afterwards discussed, and sometimes by stoppage of the pulmonary circulation through minute emboli.

Alterations in the oxygen-carrying power of the blood will be discussed presently, and those in the external respiration subsequently.

Oxidation of Protoplasm.—The movements of protoplasm are intimately connected with processes of oxidation going on in it.

By these processes chemical energy is converted into the mechanical energy exhibited in the movements, and this is sometimes very considerable.

The oxygen which takes part in these processes is not always derived from the surrounding medium at the exact moment when

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[1] For further details see *Physiological Chemistry*, by A. Gamgee, vol. i., 1880, p. 130.

the movements take place ; it may have been obtained some time before, and the movements may continue for a little while after all oxygen has been removed.

It therefore appears that protoplasm has the power of absorbing and storing up within itself, in some manner or other, oxygen, which it can afterwards utilise for the purpose of liberating mechanical energy.

This **storage of oxygen** takes place not only in the protoplasm of unicellular organism, but also in the tissues of the higher animals, *e.g.* the muscles.

The exact way in which storage occurs is not known, but it has been well compared by Professor Ludwig to the storage of oxygen in gunpowder. The oxygen is there contained in the nitrate of potassium, a compound which is readily decomposable by the application of heat, and then gives rise to the evolution of mechanical energy ; and this it does perfectly well in an enclosed space, like a gun-barrel, where no air is present.

The power of storing up oxygen is very limited, and although protoplasmic movements continue for a little while after all external oxygen has been removed, yet they will not continue long.

A convenient way of ascertaining this fact has been devised by Kühne, who adds a small quantity of blood or of hæmoglobin solution to a drop of water containing protoplasmic organisms or cells placed on a covering-glass. This is then observed with a micro-spectroscope. The hæmoglobin solution exhibits the two bands characteristic of oxy-hæmoglobin. When all the oxygen is removed by means of a stream of hydrogen, kept up for some time, the spectrum of oxy-hæmoglobin passes into that of reduced hæmoglobin.

The occurrence of this change indicates the moment when all the oxygen has disappeared from the liquid. By reckoning from this moment onwards, we are able to estimate the length of time during which the movements continue in the absence of oxygen.

Oxygen-carrying Power of Protoplasm.—Not only does protoplasm possess the power of taking up oxygen readily and assimilating it to itself, but it has also the power of taking up and giving off oxygen to other substances when these substances would be unable to take it themselves.

We may understand this action better by comparing it in a very rough way with that of a man whose greater strength enables him to seize fruit or break off pieces of sweatmeat and give them to his child, which thus enjoys what it could not have obtained for itself, however desirous of them it might be.

Method of Experimenting.—Guaiac resin, when finely divided and oxidised, becomes of a blue colour. It has, however, only a slight power of attracting oxygen to itself from the air, or from water in which the oxygen is dissolved, and thus the blue colour is developed slowly.

On the addition of protoplasm to the water containing the guaiac, the blue colour is developed rapidly. The reason of this possibly is, that the protoplasm has taken up oxygen from the water and given it over to the guaiac. This process reminds us of the action of spongy platinum in causing oxidation of hydrogen or formic acid.

Ozonising Power of Protoplasm.—It has been supposed that, in addition to its power of oxidising such substances as guaiac by giving to them oxygen which it has already taken up, protoplasm has the power of actually breaking up the molecules of oxygen and forming ozone.

The rapid oxidation which protoplasm causes has been attributed to this power. A similar action to this is observed during the slow oxidation of phosphorus. Phosphorus appears to break up the molecule of oxygen, taking to itself one atom and freeing another, which unites with two more in order to form ozone.

Action of Drugs on Oxidation.—A convenient way of testing the effect of drugs upon oxidation is to use the protoplasm of potato, of lettuce, or of dandelion. The most active part of the potato lies just under the skin, as is seen by pouring some freshly prepared tincture of guaiac over its cut surface. A ring of blue first forms close to the skin, and is always darkest there, although it may extend over the whole of the cut surface. The ammoniated tincture of the British Pharmacopœia will not answer. The tincture must be made with spirit only. When potato is used, the whole of the potato may be pounded with water, or, still better, the peel alone may be cut off and rubbed up with water in a mortar and then filtered through linen. When lettuce or dandelion is used, the fresh leaves are triturated

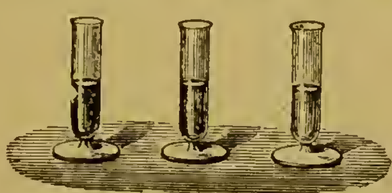

FIG. 11.—Test-glasses for examining the action of drugs on oxidation.

in a mortar with five or ten times their bulk of water, and the solution is then filtered. A row of test-tubes or test-glasses having been prepared, a measured quantity of water is put into the first. In this glass the protoplasm is not mixed with any foreign substance, and it therefore serves as the standard with which to compare the others; and into the others is put a similar quantity of solutions of the drugs to be tested. Each test-glass is distinguished by a label bearing either a number or the name of the drug which it contains attached to it. To each glass a measured quantity of the lettuce-water is added and the contents mixed by shaking. All are allowed to stand for a period varying from a few minutes to some hours. Then a small drop of freshly-prepared tincture of guaiac is added to each, mixed by shaking, and allowed to stand for one or two minutes; the glasses are then arranged in the order of depth of colour.

In this way it is found that many drugs greatly lessen or almost completely abolish the oxidising power of protoplasm, so that while the lettuce-water in the standard glass assumes a dark-blue colour, that in the others exhibits varying shades of blue, or may even retain the creamy-white colour caused by the guaiac without showing any blue whatever.

The colour is deeper and the reaction is more readily obtained when the tincture of guaiac is mixed with some substance capable of giving off oxygen readily, such as a solution of peroxide of hydrogen in ether, usually called ozonic ether.

A number of experiments made with potato-water by Cash and myself showed that oxidation in potato solution was diminished most powerfully by strychnine, then by quinine and coniïne; next by morphine, codeine, cinchonine, and atropine, each of which had almost exactly the same action;

next by nicotine, and then veratrine. Aconitine seemed neither to retard nor accelerate oxidation, and presented exactly the same degree of coloration as the standard solution. Caffeine, picrotoxin, and digitalin appeared somewhat to hasten oxidation.[1]

Reduction by Protoplasm.—Ehrlich[2] has shown, in an interesting manner, the properties of oxidation and reduction possessed by protoplasm. Methylene-blue, alizarin-blue, and indo-phenol are coloured bodies which become colourless on being reduced. After injecting methylene-blue into the veins, he found that most of the parenchymatous tissues became coloured, the heart, brain, cortex of kidney, the voluntary muscles, &c., while the lungs and the liver were normal and only a small amount of colouring matter could be obtained by prolonged exposure to the air. Ehrlich concluded that the indifferent paraplasma of the cells excretes the unchanged matter, while the protoplasm, which is greedy for oxygen, excretes the reduced colouring stuff.

Action of Drugs on Blood.

The hæmoglobin of blood has also the power of taking up oxygen readily and giving it freely off again. Hæmoglobin free from oxygen, or, as it is sometimes called, **reduced hæmoglobin**, is recognised by the simple band which it gives between D and E, when examined spectroscopically.

Hæmoglobin combined with oxygen, or **oxyhæmoglobin**, gives two bands, situated in nearly the same portion of the field of the spectroscope. These are separated from one another by a clear space, and are more sharply defined and darker than the spectrum of hæmoglobin.

The oxygen of oxyhæmoglobin may be replaced by other gases. Thus:—**Carbonic oxide** drives out the oxygen from oxyhæmoglobin and forms carbonic oxide hæmoglobin (CO-hæmoglobin). This is a comparatively stable compound. It presents spectroscopic bands nearly the same as those of oxyhæmoglobin, but which are slightly nearer to the violet end of the spectrum. This compound, being stable, circulates in the blood without performing the functions of respiration. It neither takes up oxygen in the lungs nor gives off oxygen to the tissues.

Animals poisoned by CO therefore die of asphyxia, the internal respiration being arrested, and their blood remains for a long time of a florid colour.

Hydrocyanic acid appears also to form a compound with hæmoglobin, which is much less stable than that of carbonic oxide. There has been a good deal of discussion about this

[1] *St. Bartholomew's Hospital Reports*, 1882.

[2] Ehrlich, 'Zur biologischen Verwertung des Methylen-Blau,' *Centralblatt f. die med. Wissenschaft.* 1885, No. 8.

compound, and its existence, indeed, has been denied. The spectrum of this compound consists of a single band resembling reduced hæmoglobin, but nearer the violet end of the spectrum.

Solutions of hæmoglobin when boiled are completely decomposed into hæmatin and a proteid body or bodies.

Hæmatin gives a single band, which differs according as the solution is alkaline or acid, and according as the solvent is water or ether.

Acids split up hæmoglobin into hæmatin and a proteid. It is sometimes possible to get these to recombine and to again form hæmoglobin, but this is far from being always the case.

Methæmoglobin appears either to be a product of the incomplete decomposition of hæmoglobin or of its excessive oxidation. Some think that it contains more oxygen than hæmoglobin, but less than oxyhæmoglobin. Others think that it is a peroxyhæmoglobin containing more oxygen than oxyhæmoglobin. At all events the oxygen is more firmly combined in methæmoglobin than it is in oxyhæmoglobin.

This body is distinguished by a spectroscopic band nearly in the same place as that of the acid hæmatin.

When the solution is made alkaline by ammonia this band disappears, and is replaced by another fine one near D.

Methæmoglobin appears to be converted again into hæmoglobin by the action of reducing agents and subsequent oxidation. When its solution is treated with reducing agents, it shows the spectrum of reduced hæmoglobin; and on shaking this with air oxyhæmoglobin is formed, as shown by the appearance of its characteristic bands.

When blood is allowed to stand for a length of time, it assumes a brownish colour and gives the bands of methæmoglobin. When **nitrites** are mixed with freshly-drawn blood, they impart to it a chocolate colour, and it then exhibits the bands of methæmoglobin.

As the oxygen in methæmoglobin is more firmly combined with it than in oxyhæmoglobin, substances such as the nitrites interfere with internal respiration, and thus in large doses will cause symptoms of asphyxia; but their action differs from that of carbonic oxide in one very important particular, viz., that it is altered by asphyxia; whilst that of carbonic oxide is not. Reducing substances are constantly present in the blood and tissues, and these accumulate to a greater extent during the process of asphyxia. Carbonic-oxide hæmoglobin, being a stable compound, remains unaffected by these, and the blood continues to circulate unchanged.

But methæmoglobin, which is produced by the action of the nitrites, becomes reduced by these substances and forms the normal reduced hæmoglobin ordinarily present in venous blood. When this reaches the lungs it again takes up oxygen, forming

normal arterial blood, by which the internal respiration is again restored. Thus, unless new supplies of nitrites are constantly added to the blood, the asphyxia they occasion quickly passes away. That caused by carbonic oxide, on the contrary, is much more permanent. It is not removed by artificial respiration, and in order to save the life of the animal or person poisoned by it, a quantity of the poisoned blood must be withdrawn from the veins and healthy blood introduced by transfusion.

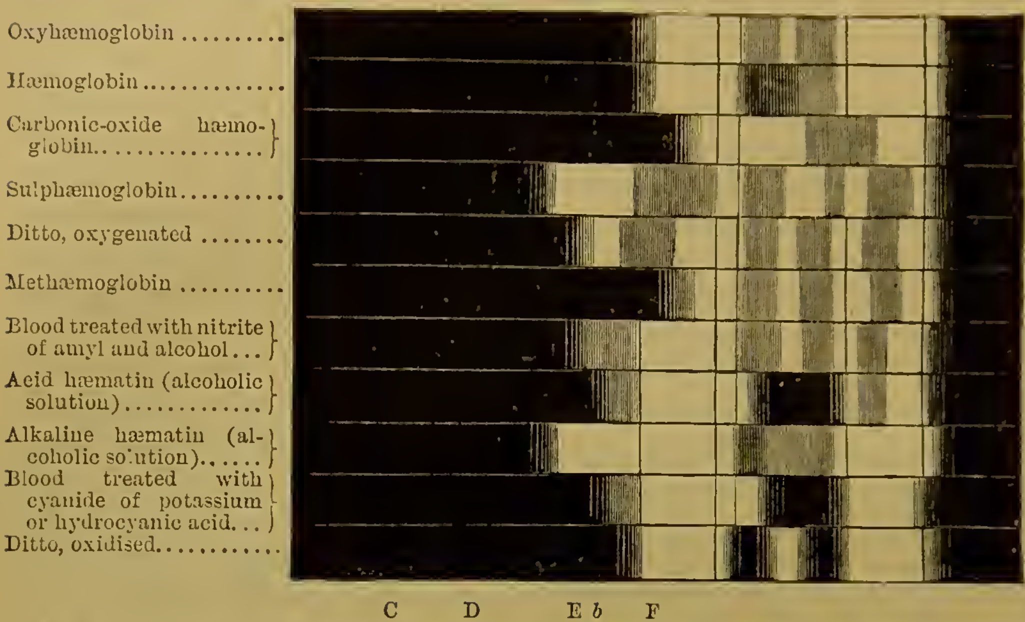

FIG. 12.—Chart showing the spectroscopic absorption-bands of hæmoglobin and its derivatives. (After McMunn.)

A method of ascertaining the effect of drugs on **oxidation** in the **blood** consists in estimating the rate at which **acid** is developed in it after its removal from the body.

In this way Binz and his scholars, Zuntz, Scharrenbroich, and Schulte, have found that both quinine and sodium nitropicrate stop the formation of acid; cinchonine lessened it.[1]

The alterations effected in the **interchange** between **blood** and the **air** have also been observed by simply allowing the blood mixed with the drug to stand for a certain time in a closed receiver, partially filled with air, and afterwards analysing the gases which the receiver contains at the end of the experiment.

By this mode of experimentation, Harley [2] found that hydrocyanic acid diminished or arrested the processes of oxidation in the blood. Alcohol, chloroform, quinine, morphine, nicotine, strychnine, and brucine, all had a similar action, though varying in extent, all of them diminishing both the amount of oxygen absorbed and of carbonic acid given out.

Uric acid and snake poison had a contrary effect, increasing

[1] A very complete list of the literature of this subject is given by Binz in his work, *Das Chinin*, Berlin, 1875.
[2] Harley, *Phil. Trans.*, 1865, p. 678.

the absorption of oxygen and the evolution of carbonic acid. Curare appeared to lessen the absorption of oxygen, but increased the evolution of carbonic acid. Mercuric chloride lessened the carbonic acid, but increased the absorption of oxygen. Arsenious acid and tartar emetic diminished the absorption of oxygen, but arsenious acid appeared also to lessen the evolution of carbonic acid, while tartar emetic appeared to increase it.

Catalysis.—Fermentation.—Inorganic Ferments.

There are many examples of chemical reactions which only occur between two bodies when a third is present, which may nevertheless be found unchanged at the end of the process. Notwithstanding the fact that the third body is found unchanged at the end of the process, it may have undergone changes during the continuance of the process. Thus alcohol is not converted into ether and water by boiling alone, but it does undergo this conversion by boiling with sulphuric acid. The acid is found unchanged at the end of the process, but is changed during it into ethyl-sulphuric acid, which, combining with alcohol, again yields sulphuric acid along with ether.

In other cases, however, we cannot show that the substance has undergone change. Thus starch is converted into dextrin and sugar and cane-sugar into grape sugar by boiling with acids, but we do not at present know that the acid has undergone any change during the process as it does in the preparation of ether. Peroxide of hydrogen is rapidly decomposed by finely divided platinum or silver, and finely divided platinum will, on the other hand, cause oxygen and hydrogen to unite rapidly. Such actions, where the third substance seems to act by its mere contact with the other substances, and without undergoing change itself, are called **catalytic**. They are probably due to an attraction of some kind bordering both on chemical and physical between the molecules.

Thus some organic substances would resist the oxidising action of the air for a considerable time, but they are readily oxidised by charcoal. It is usually said that the charcoal has the power of attracting oxygen and condensing this gas upon its surface. It does not unite with the oxygen chemically so as to form CO_2, but merely attracts it, holds it for a while, and then gives it off readily to any oxidisable substance. Platinum, palladium, rhodium, and iron absorb hydrogen, palladium doing so to an enormous extent, especially when it is in a spongy form. The hydrogen is supposed by some to be simply condensed within the metal, while others think that the hydrogen and metal unite to form a hydride. The hydrogen is given off from the metal in a nascent form, and has very strong affinities.

Thus palladium-hydrogen readily reduces ferric to ferrous salts, the hydrogen taking oxygen from the ferric salt and forming water. But when the hydrogen is liberated from palladium or rhodium in presence of oxygen, it appears to convert the oxygen into ozone, and greatly increases its oxidising power. Thus palladium-hydrogen with oxygen colours a mixture of potassium iodide and starch paste blue, and oxidises hæmoglobin to methæmoglobin and ammonia to nitric acid. Spongy rhodium, or iridium saturated with hydrogen, cause formic acid to be oxidised to carbonate, calcium formate being changed into calcium carbonate. Exactly the same action is possessed by an organic ferment, and in the conversion of the formic into carbonic acid the ferment and the spongy rhodium or iridium are alike unchanged. Spongy platinum, palladium, rhodium, and iridium may thus be regarded as **inorganic ferments.**[1]

Ferments Organic and Organised.

The mechanical energy displayed in the movements of protoplasm is supplied by processes of chemical change, and chiefly of oxidation.

By these processes some of the substances contained in the protoplasm are destroyed, and their place must be supplied by fresh material. This material is obtained from the food, but, in order to render it available for the protoplasm, its atoms must be more or less disintegrated in order that they may again be assimilated. As Hermann very well puts it, the bricks of which the old house is built must be pulled asunder before they can be

FIG. 13.—An amœba figured at two different periods during movement. *n*, nucleus; *i*, ingested bacillus.

built up again into the new. In the present case, the bricks are the atoms of protoplasm in some other organism living or dead, which is being used as food by some larger mass of protoplasm, as, for example, a bacillus which has been absorbed by an amœba. (Fig. 13.)

In order to render the protoplasm in the bacillus available for the nutrition of the amœba, the atoms of which it is composed

[1] Hoppe-Seyler, *Ber. d. deutsch. chem. Gesellsch.*, 1883, Feb. 12, p. 117.

must be, to some extent, decomposed. This process appears to be effected by enzymes or, as they are sometimes called, organic ferments.

Ferments are bodies which split up carbon compounds at moderate temperatures and lead to the formation of other carbon compounds, most of which are of a simpler constitution than the first.

In this definition we require to introduce the term 'moderate temperature,' because excessive heat alone will cause the atoms of a complex carbon compound to fly asunder and form simpler compounds, as in the process of dry distillation. A less heat than this, but aided by the action of powerful chemicals, will also produce the same effect. For example, fibrine heated with diluted hydrochloric acid under pressure yields peptones; but the same change is effected at the temperature of the mammalian body by the aid of pepsin. Trypsin from the pancreas effects a similar change when mixed with water alone without the aid of an acid, though its action is certainly aided by alkalies. Neither pepsin nor trypsin are alive, but they contain carbon, and are therefore called **organic ferments.** But this term easily leads to confusion with ordinary living or organised ferments, and so the term **enzymes** has been lately introduced to signify ferments such as diastase, ptyalin, and pepsin, which, though they contain carbon and are therefore called organic, are not alive and have no definite structure, or, in other words, are not organised. The term **unformed ferments** has also been applied to them.

By **organised ferments** we mean minute living organisms, which in the course of their life-processes cause decomposition of the substances in which they live. They have also been called **formed** ferments. Examples of these are yeast and bacteria.

The processes of **fermentation** have been divided by Hoppe-Seyler into **two kinds**:—

(1) Those in which water is taken up; and (2) those in which oxygen is transferred from the hydrogen to the carbon atom.

The hydration in the **first** case is produced by the ferment acting either (*a*) like a dilute mineral acid at a high temperature, as in diastatic and invertive ferments and in the decomposition of glucosides; or (*b*) like caustic alkalies at a high temperature, as in the splitting up of fats or the decomposition of amide compounds. These processes of fermentation by hydration are chiefly carried on by enzymes.

The **second** class of fermentative changes by the transference of oxygen from the hydrogen to the carbon, as in lactic and alcoholic fermentation and in putrefactive processes, are chiefly produced through the agency of organised ferments. The action of the latter may be to a certain extent imitated by spongy platinum, which absorbs oxygen readily, and readily gives it off again to oxidisable substances. Thus acetic fermentation usually

produced by an organised ferment may be also brought about by spongy platinum.

The **products** formed by the action of organised ferments on the media in which they live are poisonous to them; and when these products accumulate above a certain proportion, they kill the ferments. Just as a fire will be smothered in its own ashes, or an animal in a confined space will be poisoned by the carbonic acid which it has itself produced, so the yeast plant, when living in a solution of sugar, is killed by the alcohol which it produces, as soon as this amounts to 20 per cent.; and other organised ferments have their lives limited in a similar way.

Action of Drugs on Enzymes.—Although, with the exception of a kind of pepsin in the naked protoplasm of *Æthalium septicum*, a species of myxomycetes,[1] enzymes have not been shown to be present in the protoplasm of the lowest organisms, it is probable that the processes of life in all living beings from the lowest to the highest are carried on by their means. A ferment, which is evidently of the greatest importance in the animal economy, has been recently discovered in the blood by Schmiedeberg. He has given to it the name of Histozyme, and he believes that its function is to split up nitrogenous substances preparatory to their oxidation.[2] The chief enzymes are the following:—

Diastatic or Amylolytic	Which convert starch and amyloids into maltose .	Diastase from malt. Ptyalin from saliva. Amylopsin from pancreas. Other ferments having a similar action from other parts of the body.
	Which convert maltose into glucose . . .	From small intestine.
Inversive Ferments	Which convert cane sugar into dextrose and levulose	Invertin from the intestinal juice. " " mucus of the mouth. " " tissue of the testis.
	Which decompose glucosides	Emulsin from bitter almonds. Myrosin from mustard.
	Decomposing sugar . .	Rennet.
	Decomposing fats . .	From stomach. From pancreas (Stearopsin).
Proteolytic Ferments	Which decompose proteids and form peptones .	Pepsin from stomach. Trypsin from pancreas. Others from saliva. Histozyme.

The action of drugs on enzymes is ascertained by taking two portions of a solution containing the enzyme and the substance to be acted upon. To one of these a quantity of the drug to be tested is added, the other acts as a standard with which to compare it. If the drug is in solution, a corresponding quantity of water must be added to the standard solution in order that both may be alike. They are then placed in a warm chamber and the rapidity of digestion is noted.

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[1] Krukenberg, *Untersuch. a. d. physiol. Inst. d. Univ. Heidelberg*, Bd. II., 1878, p. 273.

[2] Schmiedeberg, *Arch. f. exper. Path. u. Pharm.*, Bd. xiv. S. 379.

The effect of some of the more important drugs on the action of enzymes will be readily seen from the following table from Wernitz, quoted by Meyer.[1] In it the proportion is shown of the drugs which arrest in watery solution the action of enzymes; thus, one part of chlorine in 8,540 parts of a watery solution will arrest the action of ptyalin upon starch paste, while creasote has no action on it even in saturated solution, and corrosive sublimate is so enormously destructive as to arrest its action, even in one part in 52,000.

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[1] Hermann Meyer, 'Ueber das Milchsäureferment u. sein Verhalten gegen Antiseptica,' *Inaug. Diss.* Dorpat, 1880.

	Emulsin	Myrosin	Diastase	Invertin	Ptyalin	Pepsin	Pancreatin	Rennet
Chlorine	1:35614	1:38888	1:7411	1:5980	1:8540	1:27167	—	—
Corrosive sublimate . .	1:65000	1:13000	1:50000	1:17500	1:52000	1:1766	1:21600	1:720
Iodine	1:5500	1:24070	1:4125	1:1000	1:4166	1:7817	—	—
Hydrochloric acid . .	—	—	—	—	—	—	—	—
Eucalyptus oil . . .	1:100	Acted only in excess		—	—	—	—	—
Bromine	1:12654	1:28490	1:5070	1:2840	1:5580	1:16777	—	1:31100
Mustard oil	Only lessens action in saturated solution			—	—	—	—	—
Copper sulphate . . .	1:11000	1:8100	1:6500	—	1:7500	1:110	1:6600	1:200 Has no action
Salicylic acid . . .	1:7600	1:2600	1:5100	1:166	1:1250	1:250	1:9000	1:333 No action
Sulphurous acid . . .	1:21666	1:20485	1:8600	1:1940	1:8600	1:1317	—	—
Benzoic acid	1:2100	1:1100	1:1025	1:400	1:2600	1:200	1:2600	1:300 Has no action
Chloride of lime . . .	1:36713	1:34333	1:6613	1:4950	1:6613	—	—	1:28400
Creasote	1:60	No action even in saturated solution				1:65	—	—
Thymol	1:100	Slight action, or none, even in saturated solution				—	—	—
Carbolic acid . . .	1:20	1:33	1:30	1:34	1:25	1:50	—	1:100
Borax	1:100	1:110	1:100	1:3580	1:100	—	—	1:1000
Benzoate of soda . . .	1:100	1:20 Only weakens	1:100	1:65	1:86	—	—	1:50
Turpentine water . .	1:2	—	—	—	—	—	—	—
Chloroform	Little or no action, even in saturated solution			—	—	1:60	—	—
Alcohol	1:28	1:35	1:3	1:10	—	1:6	1:3	—
Glycerine	1:3	1:2	1:2 Weakens	1:2 Weakens	1:3 Weakens only	1:3	—	—
Acetate of aluminium . .	1:50 Weakens	1:50 No action	1:380 No action	1:100 Weakens	No action	—	—	—

The different action which the same drug exerts upon formed and unformed ferments is of great importance, because upon it depends our power to use the drug in the practice of medicine. Thus creasote. which appears from the preceding table not to destroy the digestive power of ptyalin and to have but a weak action upon that of pepsin, has been found by Werneke to destroy yeast in a dilution of one part to 500 of water; and by Bucholtz to kill bacteria in a dilution of one part to 1,000 of water. This difference enables us to arrest fermentation in the stomach depending on the presence of low organisms, while the digestive action of the pepsin is not interfered with, or only very slightly. The following diagram shows the action of drugs on enzymes and on the lactic ferment, which is a bacillus.

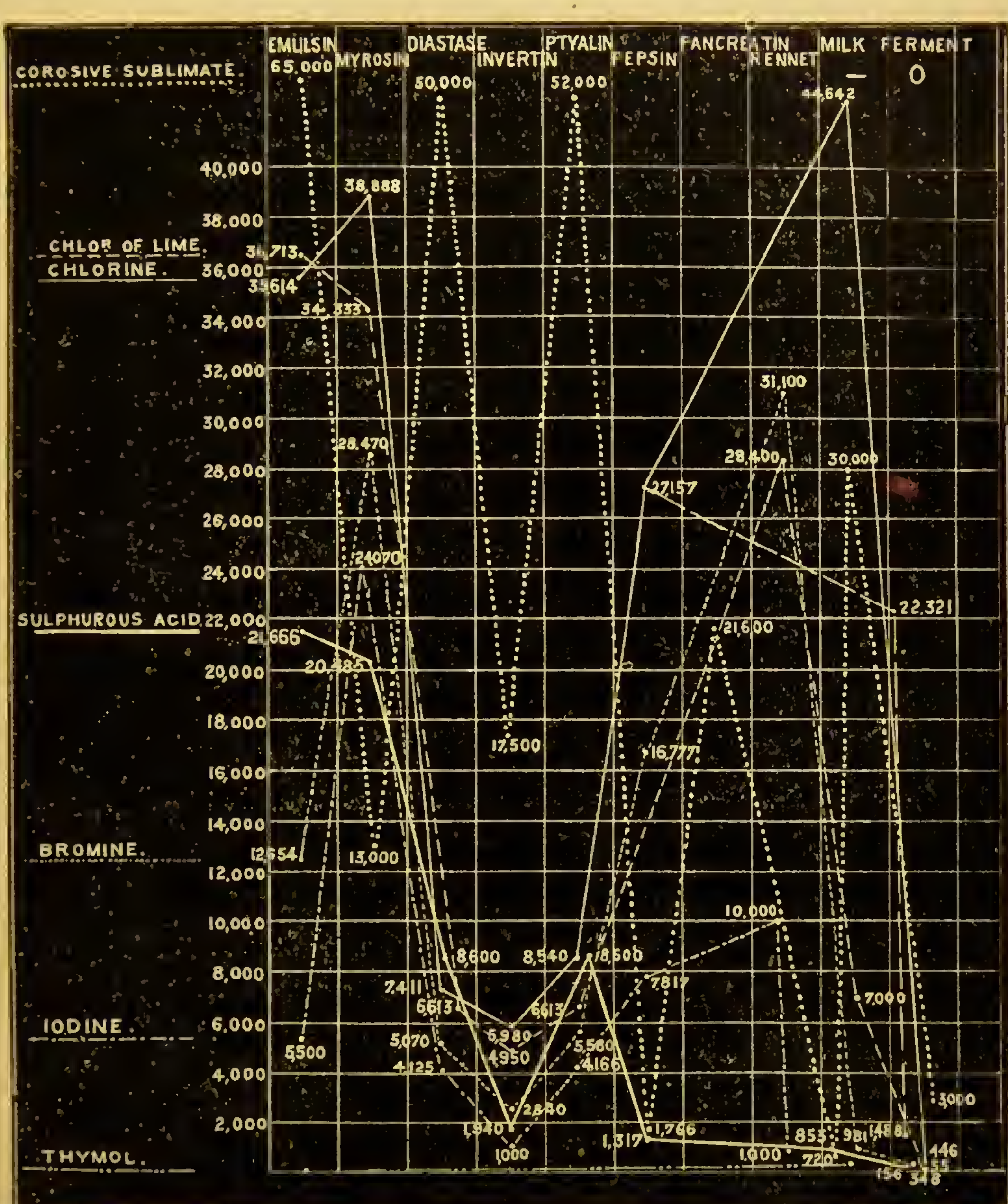

FIG. 14.—Diagram to show the different action of drugs on different enzymes. The nature of the line showing the action of each drug is shown under its name.

Zymogens.

As several enzymes act readily in neutral or slightly alkaline fluids, it is evident that if they existed free in every part of the animal body, they would soon lead to its speedy destruction. Accordingly, we find that they do not normally exist free, except at the times and places they are required.

This fact was first discovered by Kühne in relation both to the stomach and pancreas, and was announced by him in the course of lectures which he delivered at Amsterdam in 1868-69, which I attended. In my note-books of those lectures I find that he stated that there seems to exist 'a pepsin-giving substance,' because if a 'slice of stomach is thrown directly into dilute HCl of 4 parts to 1,000 of water at 40° C. no digestion takes place,'[1] a fact which shows that pepsin is not always present in it. In regard to the pancreas, he not only recognised the existence of a ferment-yielding body, but described a mode of obtaining ferment from it in the following words:—'Glands which have no action on fibrine can be made active by digesting in very dilute acid and then neutralising or alkalising, there seeming to exist a *ferment-forming* substance in the pancreas.'

Kühne's discovery of the existence of ferment-yielding bodies does not seem to have become widely known, and it was again made independently by Liversedge[2] in regard to the amylolytic ferment of the pancreas, and by Heidenhain in regard to trypsin. These observers found that when glands which did not contain ferment were exposed to the air ferments were formed.

Heidenhain[3] also investigated more fully these ferment-forming substances, and gave to them the name of zymogens.

The methods by which we **obtain ferments from zymogens** are, therefore, exposure to air and treatment with acids.

Organised Ferments.

The chief organised ferments are the **yeast**-plant, which produces alcohol and carbonic acid from grape sugar, and various kinds of **bacteria**, one of which produces butyric, another lactic, and another acetic fermentation. Both yeast and bacteria belong to the lowest class of plants, the protophytes. To this class also belong moulds, the action of drugs upon which is sometimes important, inasmuch as moulds give rise to some skin diseases.

Yeasts, moulds, and bacteria have been variously classified by different authors, and the classification is apt to undergo changes as our knowledge of the life-history of these different organisms increases.

At present it is not certainly known whether the various

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[1] Just after this there is unfortunately a blank in my notes, but Professor Kühne has kindly supplied the deficiency, and informs me that he was then speaking of slices taken from the external surface of the stomach, and therefore containing the lower ends only of the gastric glands.

[2] Liversedge (Nov. 1872), *Journ. of Anat. and Physiol.*, Nov. 1873, p. 23.

[3] Heidenhain, *Pflüger's Archiv*, Bd. xi. p. 557.

kinds of bacteria, for example, are generically or specifically different, or whether they can, by altered cultivation, be transformed into one another or not.

Koch, who has cultivated them by the dry process on gelatine instead of in liquid, and has thus been able to avoid admixture of different kinds of bacteria, has come to the conclusion that each kind possesses distinctive characters; but Klein has shown that, even when cultivated in this way, bacteria may vary much in form. Thus the bacillus anthracis may form torula-like cells, from which ordinary bacilli are again produced.

The numerous names used in treatises on the subject of organised ferments are apt to lead to confusion, hence some of the names are given here simply for the purpose of reference. Thus Brefeld's classification is :—

(1) Phycomycetes = algoid fungi; (2) Mycomycetes = true higher fungi; (3) Myxomycetes = gelatinous fungi; (4) Blastomycetes = yeast fungi; (5) Schizomycetes = bacteria.

The classification into yeasts, moulds, and bacteria which I have followed may not be botanically correct, but it is convenient for our present purpose.

Yeasts.—The yeast-plant, to which various names have been given, as torula cerevisiæ, saccharomyces, consists of ovoid cells, which multiply by budding. The buds may remain attached, forming torula-chains, but when they attain the size of the parent cell they fall off and begin to multiply anew. When placed in saccharine solutions the plant, during the process of growth, decomposes the sugar and forms alcohol and carbonic acid.

In this process oxygen is usually absorbed from the air in considerable quantities, but fermentation can occur in saccharine solutions even when oxygen is excluded, though under such conditions the torula grows slowly. When plenty of oxygen is present, and the layer of fluid shallow, the torula grows luxuriantly, but there is very little fermentative change; while, on the other hand, when free oxygen is excluded the torula grows slowly, but there is marked fermentation.

Another plant nearly allied to yeast is the mycoderma vini, the ferment which changes alcohol into acetic acid. The mycoderma is not regarded by Naegeli as a species distinct from torula, and it is considered by Grawitz to be the same as the fungus found in the aphthous patches which occur about the mouth and throat of children suffering from thrush, although this fungus is usually said to be an oïdium.

To test the action of drugs on alcoholic fermentation, equal quantities of a solution of grape sugar with yeast are introduced into two test-tubes, and to one of them a little of the substance to be tried is added. These are then inverted over mercury and kept in a warm place for several days. The amount of gas developed is then measured, and the power of the drug to prevent fermentation is estimated by the diminution in the amount of carbonic acid produced, as compared with the standard.

Mould Fungi, or Hyphomycetes.—These form long filaments or hyphæ, which become agglomerated into a mycelium or mass of compact tufts. They multiply not only by gemmation, but by the formation of spores.

These moulds vary considerably according to the soil in which they grow, and the amount of oxygen present. Thus, if the spores of the common white mould, *Mucor mucedo*, are sown in a liquid containing sugar and exposed to the air, they grow on the surface, forming branched hyphæ without septa, and the liquid absorbs oxygen. But if the mycelium be immersed, or the oxygen withdrawn, septa develop in the hyphæ, and they break up into segments which multiply by budding, forming a kind of yeast with large cells, and, like the true yeast, decomposing sugar into alcohol and carbonic acid.

They may be trained to thrive on substances on which they do not usually grow by gradually altering the composition of the soil. Thus, the commonest of all moulds, *Penicillium glaucum*, although it does not usually grow on blood, may be trained to do so by transplanting it from bread to peptone, and then to blood.

Heat destroys these fungi, but a much higher temperature is required to kill the spores than the perfect plant, and in order to destroy the spores a temperature of 110°–115° C., kept up for an hour, is requisite.

The mould-fungi cause some local diseases in the body, and especially skin diseases such as favus, tinea tonsurans, tinea versicolor, tinea sycosis, onychomycosis, and the madura-foot or fungus-foot of India. They also occur in the fur of the tongue.

Bacteria, or Schizomycetes.—Bacteria are every day becoming more and more important on account of the relation in which they are found to stand to various **diseases.** Anthrax, diphtheria, phthisis, and typhoid fever, are probably all due to various species of bacteria introduced into the body, and affecting various organs in it. It is, therefore, of the greatest possible importance that their life-history should be learned, and that we should know what the conditions are under which they thrive best, and what the conditions are which will destroy their life and prevent their development.

They appear to increase in two ways: first, by simple multiplication of their parts, and secondly, by forming spores.

Bacteria require water, organic matter, and salts, for their life. Some of them also require the presence of free oxygen; others do not; hence they have been divided by Pasteur into two classes: **aërobious** and **anaërobious.** To the anaërobious bacteria oxygen is not merely unnecessary but hurtful, and even the aërobious bacteria, although they require oxygen in a certain quantity, are injured or destroyed by it when it is in excess.

FIG. 15.

Blastomycetes, or Yeasts	Torula, or Saccharomyces (Fig. 15) or Mycoderma.

FIG. 16.

Hyphomycetes, or Moulds	Mucor. Penicillium. Oïdium. Achorion. Trichophyton Microsporon.

FIG. 17.

Schizomycetes, or Bacteria . .	Sphaerobacteria (globular cells) .	Micrococcus (1 (*a* & *b*) & 2, Fig. 16). Sarcina (3).	
	Microbacteria, or Bacteria proper (small, rod-like cells)	Bacterium . . .	Bacterium termo (4). B. lineola (5).
	Desmobacteria, or Filobacteria (larger rod-like or thread-like cells) . .	Bacillus (straight) .	B subtilis (6). B. anthracis (7). B. septicæmia. B. malariæ (8). B. tuberculosis (12). B. lepræ.
		Vibrio (wavy) .	Vibrio serpens (9).
	Spirobacteria (twisted or spiral cells) . . .	Spirochæta (long, flexible, close-wound spirals) . . .	Spirochæta. Obermeyeri (10).
		Spirillum (short, stiff, open spirals). .	S. volutans (11).

The soil which is most favourable to different classes of bacteria varies with each class. A **struggle for existence** goes on between bacteria and other organised ferments, and between different kinds of bacteria themselves, in the same way as amongst higher plants. Just as an abundant crop of one kind of higher plants will occupy a whole field and choke other plants, so that kind of bacterium which grows most readily in a particular soil will choke others and prevent them growing at the same time with itself. During their growth they alter the soil or substance in which they grow, either by exhausting the nutriment it affords, or by forming in it new substances which are injurious to themselves, and thus they gradually die out.

But the soil which is no longer suitable for one kind of bacterium then becomes suitable for another, and their spores, which may have lain without germinating during the time the first kind was growing, now begin to grow actively.

Thus, if a number of germs of different classes of fungi be added at the same time to a saccharine solution, the bacteria only will grow and set up lactic fermentation. If a small quantity of tartaric acid be now added ($\frac{1}{2}$ per cent.) the yeast alone will grow and alcoholic fermentation begins. If more tartaric acid be added (4–5 per cent.) the alcoholic fermentation stops, and mould begins to grow. In this process neither the bacteria nor the yeast are killed by the addition of tartaric acid, which, in different proportions, merely renders the liquid more favourable for the growth of the yeast and mould respectively, and enables them to flourish best, although the others are still present.

In fresh grape-juice many germs are present, but the composition of the liquid being more favourable to the growth of the yeast-plant than to other fungi, it alone grows. When it has converted the sugar into alcohol its growth stops, and bacteria may then multiply and convert the alcohol into acetic acid. This in turn checks the growth of the bacteria, and mould-fungi then find the soil favourable. In their growth they consume the lactic acid, and the liquid once more affords a favourable soil for bacteria, which may then grow and cause putrefaction.

The same struggle for existence occurs between the different species of bacteria themselves. Thus micrococci may be prevented from growing by micro-bacteria, and bacilli may be killed by bacterium termo when the supply of oxygen is insufficient for both.[1]

It is to be noted, however, that in the struggle for existence the formation of poisonous products by bacteria may be, and probably is, beneficial to them. No doubt these poisonous products check their own growth and finally destroy them; but

[1] Ziegler's *Pathological Anatomy*, translated and edited by MacAlister, p. 272. This work contains a very lucid and complete account of disease germs.

in the struggle for existence between bacteria and living tissues these poisons may be beneficial to the bacteria by killing the tissues, and thus giving the bacteria a more ample supply of nutriment.

In investigating any problem it is always best to take the simplest case, and if we look at the struggle for existence between bacilli and an amœba, or white blood-corpuscle, we shall see that the formation of poisonous products by the bacteria may enable them to destroy the amœba or leucocyte instead of their being destroyed by it (Fig. 25, p. 87).

These **poisonous products** in fact may prepare the soil for bacteria, and this supposition is confirmed by the observations of Rossbach and Rosenberger. Rossbach found that when papain was injected into the vessels, micrococci developed in the blood with extraordinary rapidity, the ferment seeming to have altered the blood to such an extent that it became an exceptionally favourable soil for the micrococci. A similar result was observed by Rosenberger from the injection of sterilised septic blood. In this blood the bacteria themselves were destroyed, but the poisonous substances which they had formed were present, and these seemed to have a similar action to the papain.

The struggle for existence between the Organism and the Microbes which invade it.—This has been found by Metschnikoff to occur both in the blood and the tissues. In the daphne, or water-flea, where the tissues are transparent, he has been able to observe the spores of a kind of yeast passing from the intestinal canal into the body-cavity (Figs. 18, 19). As they pass through they are attacked by leucocytes—sometimes by one, sometimes by many. These leucocytes occasionally coalesce so as to form a plasmodium. When they are sufficiently powerful they digest and destroy the spores (Figs. 19, 20, and 21). Sometimes the spores may be left sufficiently long intact to germinate and give off buds, which become free in the body-cavity, and may also, like the parent spores, be attacked and digested by leucocytes.

When there are many spores they destroy the leucocytes instead of being destroyed by them (Fig. 25).

The connective-tissue cells also take up and destroy the microbes, and, from the property the cells possess of eating up the microbes, Metschnikoff names them phagocytes.[1] He finds that bacillus anthracis is eaten up in a similar way by white blood-corpuscles;[2] and Fodor[3] has observed that various kinds of bacteria, viz. bacterium termo, bacillus subtilis, and bacterium megatherium, as well as the spores of the latter, disappear in four hours after they are injected into the blood of living rabbits;

[1] *Virchow's Archiv*, vol. xcvi., p. 177. [2] *Idem*, vol. xcvii., p. 502.
[3] *Arch. für Hygiene*, Bd. 34, p. 129.

FIG. 18.—A piece of the anterior part of the body of a Daphne, with a number of spores, some of which are still in the intestinal canal, others are penetrating the intestinal wall, and others are free in the abdominal cavity, where they are attacked by leucocytes.

FIG. 19.

1. A spore which has penetrated the intestinal wall and entered the abdominal cavity, where four leucocytes have surrounded its end. *m*, the muscular layer of the intestine ; *e*, epithelial layer ; *s*, the serous layer.
2. A spore surrounded by leucocytes from the abdominal cavity of a Daphne.
3. Confluent leucocytes enveloping a spore.
4. A spore, of which one end is being digested by a leucocyte.

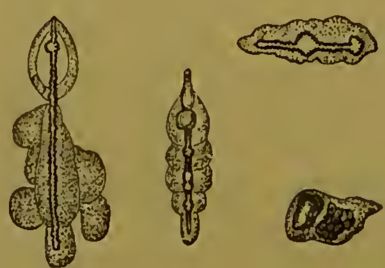

FIG. 20.—Different stages of the changes undergone by spores through the action of phagocytes.

FIG. 21.—A germinating spore with leucocyte adherent to it.

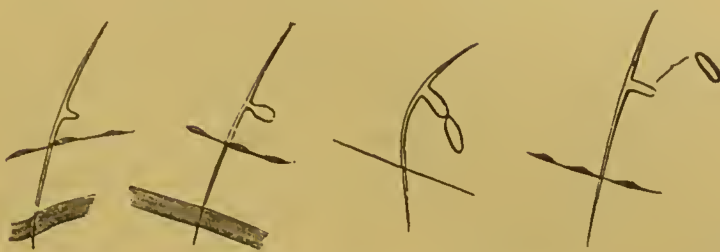

FIG. 22.—A spore germinating and forming conidia, which drop off and become free in the abdominal cavity.

FIG. 23.—*a* and *b*, two stages in the process of leucocyte eating up two conidia.

FIG. 24.—A leucocyte enclosing conidia.

FIG. 25.—A group of conidia which have caused the leucocytes surrounding a spore to dissolve, leaving only an empty vesicle and fine detritus.

FIG. 26.—A connective-tissue phagocyte, containing three fungi-cells.

FIG. 27.—Leucocyte of a frog from the neighbourhood of a piece of the lung of a mouse infected with anthrax about forty-two hours after the piece of lung had been placed under the skin of the frog's back. The leucocyte is in the act of eating up an anthrax bacillus.

FIG. 28.—The same leucocyte, a few minutes later, after it has completely enveloped the bacillus.

but if the animals are weak, or depressed by hunger or cold, they have much less power of destroying the foreign organisms, and so a longer time elapses before the bacteria disappear.

When only a small number of pathogenic bacteria, such as the bacillus anthracis, is injected into the blood at once, they are destroyed in the organism; but when they are in larger numbers, they have the best of the struggle, and the organism itself is destroyed. It is probable that bacteria are constantly entering the organisms of men and animals from the lungs and digestive canal, but unless they are excessive in number, and virulent in their nature, they are quickly destroyed.[1]

The **septic poisoning** which occurs from wounds is not due merely to bacteria entering the blood from them, but is due chiefly to the absorption of the poisons which the bacteria have formed in the wound. The dead or enfeebled tissues which occur in the wound afford a soil favourable to the growth of the bacteria, and for the formation of their deadly products. When these are absorbed they not only poison the tissues generally, but, by doing so, convert the whole body into a soil suitable for the growth and development of bacteria, as is shown by the fact that the tissues of animals killed by the injection of sepsin decompose very quickly, and swarm with bacteria shortly after death.

Action of Drugs on the Movements of Bacteria.

Mode of Experimenting.—In order to test the effect of a drug on the movements of bacteria already developed, a drop of the solution containing bacteria may be mixed, under the microscope, with a drop of the solution of a drug in the way already described at page 63, and the strength of solution necessary to destroy their movements estimated in the same manner.

In order to combine experiments on the movements, and on the reproduction, so as to ascertain whether the bacteria which have been rendered motionless by heat or drugs are really dead, or are only torpid, the covering-glass in the experiment just described is taken up with a pair of sterilised forceps, and dropped into some sterilised Cohn's solution (*vide* p. 72). It is then put along with the standard solution into a warm chamber, and left for a day or two. If the bacteria have been destroyed, it will remain clear like the standard solution, but if they have only become torpid, it will be more or less opalescent or milky.

In performing this experiment, great care must be taken that the solution of the drug has been sterilised by boiling; and that the covering-glass, glass slide, all the instruments, and indeed everything used in the experiments, have been also thoroughly sterilised by heating.

A **temperature** of 66° to 70° C. usually arrests the movements of bacteria, and if continued for an hour destroys adult organisms, though not the spores. A temperature of 100° C. usually destroys the spores as well, but this is not always the case. If the bacteria are moist, this temperature generally kills them, but not if they happen to be dry, and a much higher tem-

[1] Fodor, op. cit. p. 147.

perature is then required. They may become dry, before being killed, by a little solution containing them having flowed or spurted into the higher part of the tube or flask, where the water evaporates and leaves them dry before the temperature has been sufficiently raised to destroy them.

The bacteria grown in different fluids are not all equally sensitive to drugs.

The most destructive substances to bacteria are corrosive sublimate, chlorine, bromine, and iodine. Quinine and the other cinchona alkaloids also destroy bacteria, their power diminishing in the following order :—quinine, quinidine, cinchonidine, and lastly cinchonine.

Bebeerine is nearly as powerful, and potassium picrate is even superior to quinine when used with Cohn's solution. When bacteria are cultivated in beef-tea instead of Cohn's solution, potassium picrate is less powerful.

Sulphocarbolates and strychnine have considerable power, though a good deal less than quinine; berberin and æsculin have hardly any power to destroy bacteria at all. Sodium hyposulphite has very little action; sodium sulphate has a destructive action, but is about ten times less strong than quinine.[1]

Action of Drugs on the Reproduction of Bacteria in general.

The spores of bacteria have an enormous power of resisting agents destructive to their vitality, very much greater than that of the fully-developed bacteria. Thus it happens that a quantity of an antiseptic, which is quite sufficient not only to prevent the spores of bacteria from developing so long as they remain in it, but to destroy fully-formed bacteria, will not destroy the vitality of the spores or hinder them from germinating as soon as they are removed from the influence of the antiseptic and transferred to a proper soil.

Yet the power to destroy the vitality of the spores completely is what is required in an antiseptic, for we wish to destroy the infectious material, and prevent it from causing disease, rather than to administer substances to an animal which will hinder the germs from developing in the blood after their introduction into it; although this may be desirable when infection has already taken place.

It is therefore necessary to test the effect of drugs in destroying the germs completely.

Method of Experimenting.—This is done by adding to a fluid, containing bacteria and their spores, varying quantities of an antiseptic, and allowing the mixture to stand for a longer or shorter time. A drop of this

[1] Buchanan Baxter, *Practitioner*, vol. i. pp. 343, 350.

fluid is then introduced by a sterilised platinum wire or glass pipette into some sterilised Cohn's fluid or beef-tea. This is watched, to see whether bacteria will develop in it or not. If they do develop, it is clear that the spores have not been killed by the admixture with the disinfectant in the original fluid ; if they do not develop, then the disinfectant has been sufficiently powerful to destroy them.

The plan usually employed is to take a number of test-tubes, plug their orifices with cotton-wool, and destroy any germs that may be attached to them by thoroughly heating them to about 300° F. in a hot chamber, or in the flame of a Bunsen's lamp. They are then allowed to cool, and a small quantity of a liquid (about 5 cc.) in which bacteria readily grow is placed in each. This also must be previously thoroughly boiled, in order to destroy any germs which may be present in it. The liquid recommended by Cohn consists of ammonium tartrate one gramme, potassium phosphate and magnesium sulphate of each five grammes, calcium phosphate ·05 gramme, distilled water 100 cc. This is filtered and boiled before use. To the tubes the different agents to be tested are added, the solutions of each having been carefully sterilised by boiling, and the pipette used being superheated in each case before it is employed. If the drugs are added in solution, a similar quantity of boiled water must be added to the first tube, which is to serve as a standard. To each of them is then added a single drop of a liquid containing bacteria.

The mouths of the tubes are then stopped with the cotton-wool and placed for a few days in a warm chamber at about 40° C. The standard liquid will then be found to be opalescent or milky. The degree of the opalescence in the other tubes will be less according to the effect of the drug which has been added, in preventing the development of bacteria.

Where it has completely hindered the development, the solution will remain quite clear, and as its strength diminishes, the opalescence will become greater until it is equal to that of the standard.

In performing this experiment it is best to use one definite form of bacterium, instead of a mixture of several unknown kinds. This is referred to again in speaking of the experiments of Dr. Koch, who generally employs the micrococcus prodigiosus as an example of an organism easily acted upon, and the spores of bacillus anthracis, or of a bacillus found in earth, as examples of resistant organisms.

It is found by this mode of experiment that a smaller quantity of poison will prevent the development of bacteria than will destroy them after they are developed.

By experiments on the comparative action of different drugs on bacteria the results contained in the following table have been obtained by N. de la Croix, and these have been to a considerable extent confirmed by Koch.

It will be seen by looking at the table that the exact limit of the power of each drug to destroy bacteria is not determined, but that two concentrations of each antiseptic are given, one of which is sufficient to do it, and the other is insufficient. The disinfecting limit therefore lies between the two experiments. But the limit of disinfection is not an invariable one for each drug, as its power to destroy bacteria is modified not only by the concentration of the solution employed, but by the length of time during which it acts, and by the temperature.

	Prevent the development of bacteria taken from meat infusion.	Do not.	Prevent the reproduction of undeveloped bacteria.	Do not.	Kill developed bacteria.	Do not.	Prevent the reproduction of developed bacteria.	Do not.	Prevent development of spores in boiled meat infusion.	Do not.	Prevent reproduction of spores.	Do not.	Prevent development of spores in unboiled meat infusion.	Do not.	Prevent reproduction.	Do not.
Corrosive sublimate	1:25250	1:50250	1:10250	1:12750	1:5805	1:6500	1:1250	1:5250	1:10250	1:12750	1:6500	1:10250	1:7168	1:8358	1:2525	1:3358
Chlorine	1:30208	1:37649	1:4911	1:6824	1:22768	1:30208	1:431	1:460	1:28881	1:34589	1:1008	1:1027	1:15606	1:23182	1:1061	1:1364
Chlorinated lime	1:11135	1:13092	1:488	1:578	1:3720	1:4460	1:170	1:258	1:3148	1:4716	1:109	1:134	1:286	1:519	1:153	1:286
Sulphurous acid . . .	1:5448	1:8515	1:135	1:223	1:2009	1:4985	1:190	1:273	1:8515	1:12649	1:325	1:422	1:12649	1:16782	1:135	1:223
Bromine	1:6308	1:7844	1:769	1:1912	1:2550	1:4050	1:336	1:550	1:13931	1:20875	1:493	1:603	1:5597	1:8375	1:875	1:1153
Sulphuric acid	1:5734	1:8020	1:205	1:306	1:2020	1:3353	1:116	1:205	1:5734	1:8020	1:306	1:420	1:3353	1:5734	1:72	1:116
Iodine	1:5020	1:6687	—	1:2010	1:1548	1:2010	1:410	1:510	1:10020	1:20020	1:510	1:724	1:2010	1:2867	5:843	1:919
Aluminium acetate . . .	1:4268	1:5435	1:59	1:80	1:427	1:835	1:64	1:92	1:4268	1:4778	1:937	1:1244	1:6310	1:7535	1:478	1:584
Oil of mustard	1:3353	1:5734	1:220	1:306	1:591	1:820	1:28	1:40	1:3353	1:5734	1:77 ?	1:108 ?	1:3353	1:5734	1:40 ?	1:60 ?
Benzoic acid	1:2867	1:4020	1:50	1:77	1:410	1:510	1:121	1:210	1:2877	1:4020	1:50	1:77	1:1439	1:2010	1:77	1:121
Borosalicylate of sodium . .	1:2860	1:3777	1:303	1:394	1:72	1:110	1:30	1:50	1:1343	1:1694	1:35	1:50	1:2860	1:3777	1:35	1:50
Picric acid	1:2005	1:3041	1:706	1:841	1:1001	1:1433	1:150	1:200	1:2005	1:3041	1:200	1:300	1:2005	1:3041	1:100	1:117
Thymol	1:1340	1:2229	1:109	1:212	1:109	1:212	1:20	1:36	1:1340	1:2229	1:109	1:212	1:1340	1:2229	1:20	1:36
Salicylic acid	1:1003	1:1121	1:343	1:454	1:60	1:78	—	1:35	1:3003	1:6004	1:603	1:1003	1:1121	1:1677	1:343	1:450
Permanganate of potassium . .	1:1001	1:1433	1:100	1:150	1:150	1:200	1:150	1:200	1:2005	1:3041	1:101	1:150	1:300	1:403	1:35	1:50
Carbolic acid	1:669	1:1002	1:22	1:42	1:22	1:42	1:266	1:4	1:402	1:502	1:22	1:42	1:502	1:669	—	1:10
Chloroform	1:90	1:112	—	1:08	1:112	1:134	—	1:08	—	—	—	—	1:103	1:134	—	1:122
Borax	1:62	1:77	—	1:14	1:48	1:69	—	1:12	1:30	1:43	—	1:14	1:107	1:161	—	1:37
Alcohol	1:21	1:35	1:44	1:8	1:44	1:6	—	1:118	1:11	1:21	1:177	1:203	1:21	1:30	—	1:142
Eucalyptol	1:14	1:20	—	1:203	1:116	1:205	—	1:583	1:20	1:29	—	1:14	1:205	1:308	—	1:30
Chlorate of potassium . . .	—	1:30	—	—	—	—	—	—	—	—	—	—	—	1:13	—	—

Action of Drugs on particular species of Bacilli.

In these experiments of De la Croix, however, the nature of the bacteria experimented on was not determined, and there might be a mixture of several sorts. Koch has therefore sought to ascertain the action of disinfectants upon definite forms of microzymes by cultivating them in pure crops before applying the disinfectant. Those which he has chiefly experimented on are the red micrococcus prodigiosus, the bacteria of blue pus, and the bacillus anthracis.

The first two do not form spores, and are easily destroyed by disinfectants. The bacillus anthracis forms spores, and was therefore employed to test the action of disinfectants upon them.

Mode of Experimenting on the Action of Drugs on Reproduction of Bacilli.—In order to avoid admixture with other species, Koch cultivated the first two on slices of potato, instead of in a solution. Upon one piece of potato the unaltered microzymes were sown (control specimen), and upon the others similar microzymes which had been exposed to the action of disinfectants. If the microzymes had been destroyed by the disinfectants, no result occurred, but if not, then a crop was obtained which, in comparison with the control specimen, was more or less abundant, according as the action of the disinfectant had been less or more complete.

For the cultivation of the anthrax bacillus, Koch used as a soil gelatine mixed with some other nutritive substance, usually meat infusion and peptone sterilised and spread upon a slip of purified glass, and exposed to such a heat as just to solidify it. Koch did not use his solidified blood-serum in these experiments. This could be placed under the microscope, and the growth of bacilli observed from day to day. Middle-sized test-tubes were then partially filled with the disinfecting solutions, and silk threads, steeped in a fluid containing bacilli and then dried, were placed in them; from time to time a thread was removed from the tubes by means of a previously heated platinum wire and placed on the slide, which was then subjected to microscopical observation. In this way it was easy to determine what strength of solution, and what time of exposure to its action, were required to destroy the spores.

The results of experiments made in this way with carbolic acid were very surprising. It was to be expected that carbolic acid would readily destroy the spores, but this was not the case. A 1 per cent. watery solution had almost no action upon them even after they had been exposed to it for 15 days; 2 per cent. slightly retarded their growth, but it did nothing more; 3 per cent. killed the spores in 7 days; 4 per cent. in 3 days; and 5 per cent. in 1 day.

This comparatively slight action of carbolic acid on spores and the long time that it requires to destroy them show that it cannot be relied upon as a universal disinfectant. But it has nevertheless great power in destroying microzymes which have not formed spores.

The fresh blood of an animal which has died from anthrax contains only bacilli and no spores. When it is mixed with its own bulk of a 1 per cent. solution of carbolic acid, it can very

soon afterwards be injected into an animal without producing any marked symptoms. A $\frac{1}{2}$ per cent. solution will not do this, so that the limit lies between ·5 and ·25 per cent. of the mixture (*v.* p. 97).

The action of carbolic acid on other fully-developed microzymes, or on the spores, is almost the same as on the anthrax bacilli.

The following table gives the result of Koch's experiments with other substances, the figures indicating the number of days during which the spores had been submitted to the action of the antiseptic previous to cultivation. The black-faced figures indicate that the spores were destroyed, and their germination prevented by exposure to the disinfectant for that number of days; a * indicates that their vitality was diminished, and that the crop from them was scanty; a † indicates that their growth was retarded; *† that it was both scanty and retarded. The disinfectants are divided into three groups. The first contains the group of fluids; the second of solutions in water; and the third of solutions in alcohol, ether, or oil.

GROUP I.—FLUIDS.

Distilled water	7	15	20	35	90						
Alcohol (absolute)	1	3	5	10	12	20	30	40	50	65	110
Alcohol (1 to 1 of water)	1	3	20	30	40	50	65	110			
Alcohol (1 to 2 of water)	1	3	20	30	40	50	65	110			
Ether	1	5	8*	**30**							
Acetone	2	5*									
Glycerine	1	3	10	20	30	40	50	65	110		
Butyric acid	1	5									
French salad oil	5	30	90								
Bisulphide of carbon	1	5	10	20							
Chloroform	1	3	10	20	100						
Benzol	1	5	10	20							
Petroleum ether	1	5									
Turpentine oil	1*	**5**	**10**								

GROUP II.—SOLUTIONS IN WATER.

Chlorine water (freshly made)	1	**5**			
Bromine (2 p. c. in water)	1	**5**			
Iodine water (1 in 7,000)	1				
Hydrochloric acid (2 p. c. in water)	1	5	**10**		
Ammonia	1	5	10		
Ammonium chloride (5 p. c. in water)	1	5	10	25	
Common salt (saturated solution)	1	5	10	20	0
Calcium chloride (saturated solution)	1	5	20	40	
Barium chloride (5 p. c. in water)	5	10	45	100	
Ferric chloride (5 p. c. in water)	2†	**6**			
Potassium bromide (5 p. c. in water)	5	10	25		
Potassium iodide (5 p. c. in water)	5	10	25	80	
Corrosive sublimate (1 p. c. in water)	1	**2**			
Arsenic (1 p. c. in water)	1	6	**10**		
Lime water	5	10	15*†	20*†	
Chloride of lime (5 p. c. in water)	1†	2*†	5		
Sulphuric acid (1 p. c. in water)	1	3	10*	20*	
Zinc sulphate (5 p. c. in water)	1	5*	10*		
Copper sulphate (5 p. c. in water)	1	5*	10*		
Ferrous sulphate (5 p. c. in water)	2	6			
Sulphate of aluminium (5 p. c. in water)	1	5	12		

Alum (4 p. c. in water)	1	5	12		
Potassium chromate (5 p. c. in water)	1	2			
Potassium bichromate (5 p. c. in water)	1	2			
Chrome alum (5 p. c. in water)	1	2			
Chromic acid (1 p. c. in water)	1	2			
Potassium permanganate (5 p. c. in water)	1				
Do. do. (1 p. c. in water)	1	2			
Potassium chlorate (5 p. c. in water)	2	6			
Osmic acid (1 p. c. in water)	1				
Boracic acid (5 p. c. in water) not quite dissolved	1	2	6†	10†	
Borax (5 p. c. in water)	5	10	15		
Sulphuretted hydrogen water	1	5*			
Ammonium sulphide	1	2	5		
Oil of mustard with water	1	5	10*		
Formic acid (sp. gr. 1·120)	1	2	4	10	
Acetic acid (5 p. c. in water)	1	5			
Potassium acetate (saturated solution)	1	4	10		
Lead acetate (5 p. c. in water)	1	5	12		
Soft (potash) soap (2 p. c. in water)	1	5	12		
Lactic acid (5 p. c. in water)	1	2	5		
Tannin (5 p. c. in water)	1	5	10		
Trimethylamine (5 p. c. in water)	1	5	12		
Chloropicrin (5 p. c. in water)	1	2	6	12	
Benzoic acid (saturated solution in water.	1	5	10	45	90
Benzoate of sodium (5 p. c. in water)	1	2	5	10	
Cinnamic acid (2 p. c. in water 60 and alcohol 40 parts)	1	3	5	10	
Indol (in excess in water)	1	5	10	25	80
Skatol (in excess in water)	1	5	10	25	80
Leucin (½ p. c. in water)	1	5	10		
Quinine (2 p. c. in water and 40 alcohol 60 parts)	1*†	5*†			
Quinine (1 p. c. in water with HCl)	1	5	10		

GROUP III.—SOLUTIONS IN ALCOHOL, OR ETHER, OR OIL.

Iodine (1 p. c. in alcohol)	1*	2*			
Valerianic acid (5 p. c. in ether)	1	5			
Palmitic acid (5 p. c. in ether)	1	5			
Stearic acid (5 p. c. in ether)	1	5			
Oleic acid (5 p. c. in ether)	1	5			
Xylol (5 p. c. in alcohol)	1	5	30	50	90
Thymol (5 p. c. in alcohol)	1	6	10	15	
Salicylic acid (5 p. c. in alcohol)	1	6	10	15	
Salicylic acid (2 p. c. in oil)	5	10	20	80	
Oleum animale (Dippel's oil, 5 p. c. in alcohol)	1	5	12		
Oleum menthæ piperitæ (5 p. c. in alcohol)	1	5	12		

From this table it appears that the ordinary method of separating between formed and unformed ferments by precipitation with alcohol and solution in glycerine cannot be relied upon as a trustworthy means of separating them, since neither alcohol nor glycerine destroys the activity of formed ferments.

It is remarkable that ether and turpentine oil, which are both ozone carriers, should have such a marked action in comparison with other fluids. This is in harmony with some recent observations of Paul Bert and Regnard, who found that oxygenated water in sufficient quantity destroys the bacteria of anthrax.

The spores of anthrax bacilli resist in an extraordinary way the action of certain substances which usually are fatal to life, as hydrochloric acid (2 per cent.), salicylic acid (1 per cent.), con-

centrated solutions of chloride of sodium, chloride of calcium, metallic solutions, borax, boric acid, chloride of potassium, benzoic acid, benzoate of sodium, cinnamic acid, and quinine.

Action of Drugs on the Development and Growth of Bacilli.—In order to test the action of disinfectants on the development and growth of bacteria, Koch put into a number of small watch-glasses, or rather crystallisation-glasses with flat bottoms, a few drops of blood-serum, or a solution of extract of meat and peptone, mixed with varying quantities of the disinfectant. Into each of these a silk thread, which had been dipped in the fluid containing bacteria and dried, was placed. In one glass serum alone, without any disinfectant, was placed, in order to ascertain, by comparison with the growth which takes place in it, how the disinfectant in the other glasses had interfered with the growth of the bacilli.

In experiments of this sort a difference was found between anthrax bacilli and other microzymes. A dilution of carbolic acid, 1 in 1,250 and 1 in 850, sufficed to prevent the growth of anthrax bacilli, while a strength of 1 in 500 was required to prevent the growth of others.

Other species are therefore more resistant than anthrax bacilli to the action of carbolic acid. The following table shows the strength of various disinfectants required to hinder or entirely prevent the development of anthrax bacilli :—

Solution	Hinders	Prevents
Iodine	1 to 5,000 . .	—
Bromine	1 to 1,500 . .	—
Chlorine	1 to 1,500 . .	—
Osmic acid . . .	1 to 1,500 . .	—
Permanganate of potassium	1 to 3,000 . .	—
Corrosive sublimate . .	1 to 1,000,000 . .	1 to 300,000
Allyl alcohol . . .	1 to 167,000 . .	—
Oil of mustard . . .	1 to 330,000 . .	1 to 33,000
Thymol	1 to 80,000 . .	—
Peppermint oil . . .	1 to 33,000 . .	—
Oil of turpentine . .	1 to 75,000 . .	—
Oil of cloves . . .	1 to 5,000 . .	—
Arsenite of potassium .	1 to 100,000 . .	1 to 10,000
Chromic acid . . .	1 to 10,000 . .	1 to 5,000
Picric acid . . .	1 to 10,000 . .	—
Hydrocyanic acid . .	1 to 40,000 . .	1 to 8,000

The following are about the same strength as carbolic acid :—

Fluid	Hinders	Prevents
Boric acid . . .	1 to 1,250 . .	1 to 800
Borax	1 to 2,000 . .	1 to 700
Hydrochloric acid . .	1 to 2,500 . .	1 to 1,700
Salicylic acid . . .	1 to 3,300 . .	1 to 1,500
Benzoic acid . . .	1 to 2,000 . .	—
Camphor	1 to 2,500 . .	—
Eucalyptol . . .	1 to 2,500 . .	—
Soft soap	1 to 500 . .	1 to 5,000
Quinine	1 to 830 . .	1 to 625
Hydrate of chloral . .	1 to 1,000 . .	—
Chlorate of potassium .	1 to 250 . .	—
Acetic acid . . .	1 to 250 . .	—
Benzoate of sodium . .	1 to 200 . .	—
Alcohol	1 to 100 . .	1 to 12·5
Acetone	1 to 50 No action . .	—
Chloride of sodium . .	1 to 64 . .	—

Influence of the Solvent.—Although a 5 per cent. solution of carbolic acid in water has a well-marked destructive action on the spores, and a strong destructive action on fully-developed anthrax bacilli, a solution of the same strength in oil or alcohol has not the least disinfectant action. A similar influence with regard to iodine is observable in the previous tables.

Effect of the Fluid with which Disinfectants are mixed.—This is sometimes very marked, especially in the case of free iodine, bromine, or chlorine. These in watery solutions are powerful disinfectants, but when mixed with fluids which contain alkalies, e.g. blood-serum, they are converted into bromides, iodides, and chlorides, and their action is very greatly diminished. The action of corrosive sublimate, however, and of ethereal oils is not altered.

Influence of Temperature on the Action of Antiseptics.—The action of antiseptics is greatly increased by a high temperature. Spores of anthrax bacilli exposed to the vapour of carbolic acid at 15°–20° C. remain unchanged even after 45 days' exposure. When exposed to the vapour of carbolic acid at a temperature of 55° C. the case is very different. Half an hour's exposure does not seem to harm them at this temperature, but many are destroyed by an exposure of an hour and a half, and very few will stand 3 hours' exposure, so that probably an exposure of 5 or 6 hours would destroy the whole of them.

Alterations in Bacteria by Heat and Soil.—By careful cultivation through successive generations of a slip taken from a wild fruit-tree, the chemical processes of growth may be so modified in it that the fruit will lose its acrid character and become edible and pleasant. What is true of higher plants is true also of lower in this respect, and bacilli are much modified by the conditions under which they are cultivated; for example, Pasteur has found that the bacilli of anthrax develop and multiply in beef-tea best at 25°–40° C. Their development is retarded at lower or higher temperatures than these, and is completely arrested at 15° or 45° C. When cultivated at a temperature where development occurs with difficulty, such as 42°–43°, the bacilli no longer form resting spores, but only grow into long threads.

Fresh bacilli injected into an animal rapidly cause death from anthrax, but the longer they have been previously kept at this high temperature the more does their virulence decrease, and at the end of four or six weeks they die.

When some of the first crop of bacilli are put into fresh beef-tea, the second crop retains the degree of virulence of the first, and the third crop taken from the second, and again grown in fresh beef-tea, has exactly the same morbific power, and so on.

When the bacilli are cultivated at 35°, the microzymes not only multiply quickly, but they form spores of a definite degree of virulence, and these spores may be kept unaltered for years in

sealed tubes, whereas the threads of developed bacilli die when air is excluded.

When an animal is inoculated with anthrax bacilli whose virulence has been diminished by cultivation at a high temperature, they produce merely temporary illness instead of death. By the growth of these non-virulent bacteria in the body, its constitution appears to undergo some alteration, and virulent bacteria subsequently injected have a much less powerful action on it. If the first injection be made with bacteria having a very slight amount of virulence, the animal may still die if injected a second time with virulent bacteria, but if inoculated first with non-virulent bacteria and a second time with bacteria rather more powerful, a slight disturbance is produced by each inoculation, and a subsequent injection of virulent bacteria no longer causes death.

The changes which are produced by **inoculation** with modified anthrax or with vaccine matter in the blood and tissues, although probably very slight, are sufficient to confer on the organism **immunity** from further infection. This is usually permanent, although the immunity may diminish with the course of years, unless the advancing age of the animal in itself tends to lessen its liability to infection.

A similar immunity against infection with different bacilli is sometimes conferred by **age**. Thus young dogs are easily infected with anthrax, but old ones are not.

A difference of **species** also confers immunity. Thus rats and field-mice are not liable to infection with anthrax, while house-mice are highly so. Algerian sheep also resist infection with anthrax, while French sheep do not.

The experiments of Cash seem to show that it may be possible by the action of drugs to alter the blood and tissues in such a way as to render the animal proof against infection by pathogenic bacteria; for he has found that by the continued administration of minute doses of corrosive sublimate to animals he can render them capable of resisting the lethal effects of anthrax subsequently inoculated.[1] This is a direction in which further research is likely to yield interesting results.

Possible Identity of Different Forms of Bacteria.

It has already been mentioned that we are not quite certain whether all the species, genera, or even orders of bacteria are natural divisions, or whether the same organism under various conditions of nutrition and development may not present such different appearances as to be included in different orders and

[1] Cash: *Proceedings of the Physiological Society*, Dec. 12, 1885. *Journal of Physiology*, vol. vii.

under different names. Yet this is a matter of very great importance in regard to the causation of disease, for if it be true that organisms which are usually innocuous may undergo an opposite process to that which occurs in anthrax bacilli by cultivation, and may in certain conditions of soil be changed from innocuous into pathogenous forms, we can understand how diseases may appear to originate *de novo*.

It has been stated by Naegeli that bacteria may be so modified by cultivation as to form entirely different fermentative products. Thus he says that the bacterium which produces lactic acid fermentation in milk may be changed by cultivating it in extract of meat and sugar, so that it will no longer produce a lactic but an ammoniacal decomposition in milk. He considers also that innocuous may be transformed into virulent bacteria, and back again into an innocuous form, and Buchner thinks that he has succeeded in transforming the ordinary hay-bacillus (bacillus subtilis) into anthrax bacillus by cultivating it for a number of generations in Liebig's meat extract, peptone, and sugar. This observation is denied by Klein [1] and others, but observations which partly support Buchner and partly Klein have been made by F. Köhler,[2] who finds that while the ordinary hay-bacillus (bacillus subtilis) is not altered in its appearance by repeated cultivations, it acquires a progressive virulence which renders it so fatal to animals as to resemble the anthrax bacillus in its deadly properties.

H. C. Wood and Formad [3] have also come to the conclusion that the micrococci found in diphtheria resemble those on furred tongues in all respects excepting in their greater tendency to grow. When cultivated successively, they lose their contagious power and grow less readily. These authors, therefore, consider that circumstances outside the body are capable of converting the slower growing or common micrococcus into the rapidly growing micrococcus of diphtheria, which, when cultivated again, reverts to the common type.

Action of Bacteria and their Products on the Animal Body.—When bacteria are injected into the animal body, they produce **different effects** according to the original **nature** of the bacteria or bacilli, the conditions under which they have been cultivated, and the quantity introduced. There is probably another factor of no less importance, which, however, still requires to be investigated, viz. the **condition of the body** (p. 97) into which they are introduced. In considering the effect of an injection into the living body of a solution containing bacilli, we must be careful to distinguish between the effect of the bacilli themselves, after their introduction into the circulation, upon the

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[1] Klein, *Quarterly Journ. of Microscopic Science*, Jan. 1883.
[2] *Inaugural Dissertation* (Göttingen), 1881.
[3] *National Board of Health Bulletin, Supplement* No. 17, Jan. 21. 1882.

tissues and organs of the body, and the effect of the substances which they have already formed in the solution before their injection.

We must distinguish between those two things in the same way as we would have to distinguish between the effects of the particles of the yeast-plant and the effects of the alcohol which it had formed, if we were to inject a solution in which yeast was growing into the veins of an animal. The yeast or the bacteria would have one effect upon the animal, the alcohol or the septic products of the bacteria would have another.

Solutions of putrid organic matter containing numerous bacteria cause high fever and often death.

The course of the fever depends on the specific nature of the bacteria, e.g. septic bacteria, anthrax bacilli, &c.

It is difficult at present to ascertain exactly how far all the following diseases are due to the presence of microbes or their products; but it has been found that micrococci cause erysipelas, acute necrosis, gonorrhœa, gonorrhœal ophthalmia, contagious ophthalmia, ophthalmia neonatorum, and are present in pyæmia, puerperal fever, ulcerative endocarditis, infective myositis, and contagious pneumonia. When malignant œdema or traumatic gangrene occur, bacilli are usually found. Micrococci are also supposed by some to be the cause of vaccinia and of diphtheritic inflammation. The bacillus anthracis produces anthrax; bacillus septicæmiæ, blood-poisoning; bacillus malariæ, ague and malarious diseases; bacillus tuberculosis, phthisis; bacillus lepræ, leprosy; and another bacillus is the cause of glanders. In relapsing fever the spirochæta Obermeyeri is found in the blood, and is probably the cause of the disease.

Alkaloids formed by Putrefaction. Ptomaïnes.—From decomposing organic matter substances can be separated which have all the characters of alkaloids.

The alkaloids produced by putrefaction are usually known by the name of **ptomaïnes.** It was at one time supposed that they were different in their chemical nature from the alkaloids which occur in plants, and they were supposed to have a much greater reducing power than the latter. It was therefore proposed to distinguish between ptomaïnes and other alkaloids by the addition of potassium ferricyanide: if the alkaloid changed this into ferrocyanide, so that a precipitate of prussian blue was obtained on the addition of ferric chloride, it was supposed to belong to the class of ptomaïnes; whereas non-reduction was supposed to show that it belonged to the vegetable alkaloids. It was soon found, however, that this test was not trustworthy, for such important alkaloids as morphine and veratrine produced reduction. Later researches, especially those of Brieger, have shown that some at least of the so-called ptomaïnes are identical with vegetable alkaloids.

We may indeed now regard alkaloids as products of albuminous decomposition, whether their albuminous precursor be contained in the cells of plants and altered during the process of growth, or whether the albuminous substances undergo decomposition from the presence of microbes, either outside or inside the animal body, or by the simple process of digestion by unorganised ferments such as pepsine.

The alkaloidal products formed by the putrefaction of albuminous substances, vary according to the stage of decay at which they are produced. At first the poisonous action of these products may be slight. As decomposition advances, the poisons become more virulent; but after a longer period they appear to become broken up and lose to a great extent their poisonous power.

Muscarine, which is the poisonous alkaloid of some mushrooms, has been made synthetically by Schmiedeberg and Harnack from choline; and Brieger has obtained from decomposing albuminous substances several well-defined chemical bodies—dimethylamine, trimethylamine, triethylamine, ethylenediamine, choline, neurine, neuridine, muscarine, gadinine, cadaverine, putrescine, saprine, and mydaleïne, as well as some substances to which he has given no name. Muscarine, neurine, and choline all have a similar action, their power diminishing in the order just mentioned, choline being much weaker than the other two. They all produce salivation, diarrhœa, vomiting, dyspnœa, paralysis, and death. Muscarine and neurine in frogs produce complete stoppage of the heart in diastole; in mammals they only weaken its action. Neurine, cadaverine, putrescine, and saprine have no marked physiological action; but one alkaloid which Brieger has isolated from human cadavers in an advanced stage of decomposition appears to affect the intestine, causing enormous peristalsis, continuous diarrhœa, lasting for days, and extreme weakness. Mydaleïne, obtained from a similar source, is interesting, inasmuch as it causes a rise of temperature; for frequently we find in cases of acute disease that the rise of temperature coincides with the constipation, and is removed by purgation, so that the question arises how far the rise of temperature in such cases may be due to the absorption of poison from the intestine. Mydaleïne causes dilatation of the pupil, enormous secretion of tears, saliva, and sweat, vomiting, diarrhœa, paralysis, convulsions, twitching, dyspnœa, coma, and death.

Sepsine, which was isolated by Bergmann and Schmiedeberg from putrefying yeast, causes vomiting, diarrhœa, and bloody stools; but Nicati and Rietsch[1] have produced choleraic symptoms in animals by cultivations of Koch's comma bacillus from which the organisms themselves had been removed; and somewhat

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[1] *Compt. rend.*, xc. 928.

similar results were obtained several years ago by Lewis and Douglas Cunningham with cholera stools in which any organisms present had been destroyed by boiling.

The extract from putrefied maize has a tetanic and narcotic action, which appears to be due to two different substances. These are not present in the same proportion, so that sometimes the tetanising action, and at other times the narcotic action, is most marked.

Another alkaloid, resembling atropine in its action, has been separated by Sonnenschein and Zuelzer from decomposing animal matter; and this has also been found in the bodies of persons dying from typhus fever.

Another which resembles curare in its action has been separated by Guareschi and Mosso [1] from putrefying brain.

Another substance causing tetanic symptoms has also been obtained from animal matter.

Leucomaïnes.—Gautier, to whom much of our knowledge regarding alkaloids produced by albuminous decomposition is due, has given the name of leucomaïnes to alkaloids which are not produced by putrefaction due to bacteria, but are formed by the decomposition of albuminous matters in the normal processes of waste in the living animal tissues. Amongst these he reckons various substances formed in muscles and allied to xanthine and creatine.[2]

Brieger has shown that during the digestion of fibrin by pepsin an alkaloid has been formed, to which he gives the name of peptotoxin.

Absorption and Elimination of Ptomaïnes and Leucomaïnes.—It is probable that a considerable production of alkaloids takes place in the intestine, both when the digestive processes are normal and more especially when they are disordered; at the same time alkaloids are being formed in the muscles, and possibly also in other tissues. Were all the alkaloids to be retained in the body, poisoning would undoubtedly ensue, and Bouchard considers that the alkaloids formed in the intestine of a healthy man in twenty-four hours would be sufficient to kill him if they were all absorbed and excretion stopped. He finds that the poisonous activity of even healthy human fæces is very great, and a substance obtained from them by dialysis produced violent convulsions in rabbits. When the functions of the kidney are impaired, so that excretion is stopped, uræmia occurs, and Bouchard would give the name of stercoræmia to this condition, because he believes it to be due to alkaloids absorbed from the intestines He also thinks that the nervous disturbance which occurs in cases of dyspepsia is due to poisoning by ptomaïnes. That

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[1] *Les Ptomaïnes*, Turin, 1883.

[2] *Sur les alcaloïdes dérivés de la destruction bactérienne ou physiologique des tissus animaux.* Paris: G. Masson. 1886.

alkaloids are excreted by the urine has been shown by Bocci, who has found in the urine a substance having an action like that of curare.

Effect of Drugs on the Action of Bacteria in the Animal Body.

So long as bacteria are outside the body, we may use drugs of any strength we please to destroy them, but the case is quite different when they have once gained entrance and are no longer outside but inside the body, because then the nature of the drug and the amount we can employ is limited by its effect on the organism itself, and we cannot administer very large doses of antiseptics lest we should injure or kill the patient at the same time that we destroy the bacteria which are causing the disease. All that we can hope to do is to **turn the scale**, if possible, in favour of the organism in the struggle for existence between the cells which compose it and the bacteria which have invaded it (*vide* pp. 86 and 89).

Our hope of doing this rests on the fact that drugs which may be injurious both to the tissue and to the bacteria are **not** equally so to each. Thus excess of temperature is injurious to the organism, but it is also destructive to bacteria; and, as Fokker[1] has pointed out, the febrile reaction which occurs on the introduction of bacteria into the blood may be a means of destroying the microbes and preserving the animal. There is often a germ of truth in apparently foolish plans of treatment, and the old practice of treating scarlet fever, small-pox, and measles by warm drinks, hot rooms, and abundant clothing may have been a blind effort to aid the natural processes of cure, just as the irritating ointment of the Middle Ages seems to have been an attempt at antiseptic surgery. The extraordinary destructive power of corrosive sublimate, and the fact that it continues to act in blood-serum just as it does in distilled water, seem to indicate that it might be used to destroy bacilli in the body, especially as Schlesinger has found that it may be injected subcutaneously into rabbits and dogs daily for several months without doing them any harm, even in doses of 5 milligrammes, 1 cc. of a $\frac{1}{2}$ per cent. solution. Koch's experiments on this point, by the administration of sublimate after inoculation with anthrax, led to a negative result, the animals inoculated with anthrax dying of the disease, notwithstanding the injection of the sublimate. On the other hand, Cash has succeeded in preventing death from anthrax by administering corrosive sublimate for some time previous to inoculation (p. 97).

The extraordinary effect of **allyl alcohol**, and the less power-

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[1] International Medical Congress, 1881.

ful but still great action of **ethereal oils**, indicate, however, that we may look forward with hope to the discovery of some organic substances which may so hinder the development of bacteria in the body after their inoculation, as to allow of their gradual destruction in the organism, and prevent the sickness or death which they would otherwise have occasioned.

In relation to this, the observations of the late Dr. W. Farr in his Report are very interesting: 'Alcohol appears to arrest the action of zymotic diseases, as it prevents weak wines from fermenting; like camphor, alcohol preserves animal matter—this is not now disputed. But may it not do more? May it not prevent the infection of some kinds of zymotic disease?'

Experiments have shown that alcohol itself has but a slight power in destroying bacilli, but it is possible that even the slight traces of the ethers which are present in wine or spirits may have some beneficial action in cases of septic poisoning.

Antiseptics, Antizymotics, Disinfectants, Deodorizers.

These classes of remedies are often confounded together. It is well, however, to distinguish their meanings:—

Antizymotics are remedies which arrest fermentation.

It has already been mentioned (p. 73 *et seq.*) that fermentative processes may depend upon either enzymes or organised ferments, and that organised ferments may be subdivided into several classes, such as those consisting of yeast, innocuous bacteria, and pathogenic bacteria.

The class of antizymotics includes all substances which arrest fermentative processes due to these bodies. It contains two subclasses: antiseptics and disinfectants.

Antiseptics are remedies which arrest putrefaction. They do this by preventing the development, or completely destroying the bacilli on which septic decomposition depends.

Disinfectants are remedies which destroy the specific poisons of communicable diseases. Many of those poisons, perhaps all of them, belong to the class of microbes, and so disinfectants may be regarded as a sub-class of antizymotics.

Deodorizers or **deodorants** are remedies which destroy disagreeable smells. Such smells often accompany the decomposition of various organic substances, which septic organisms cause. These foul-smelling products may be injurious to health in themselves by acting as poisons; but they are not to be confounded with the bacteria which produce them. Moreover, the disagreeable nature of the smell is not always to be relied upon as an index of its poisonous nature. M. Gustav le Bon made some experiments with hashed meat and water, over which he put some small animals. As the meat decomposed, the liquid teemed with organisms, was very fatal when injected into an animal,

and emitted a very foul smell, which, however, did not seem to be very injurious. Afterwards the organisms present in the liquid died, and the foul smell became much less disagreeable; but the emanations from the liquid appeared to become much more poisonous, although the liquid itself, when injected into an animal, had no longer the same virulent power as at first.

Uses of Antiseptics.—Antiseptics are employed externally in order to destroy microbes before their entrance into the body, and are administered internally with a like object, or for the purpose of at least preventing the free development and multiplication of the microbes.

They are employed externally in **surgical operations**, with the object of destroying any organisms which might find a nidus in the wound, and there give rise to the formation of poisonous substances. Both these substances and the bacteria themselves will not only have an injurious local action in the wound, but by undergoing absorption may prove injurious or fatal to the organism as a whole. The antiseptic plan of treatment has been empirically practised in a limited manner for a very long period without its principle being recognised: for the well-known Friar's balsam has antiseptic properties. It is to Lister that we owe the introduction of such a mode of treatment, not based upon mere empiricism, but upon scientific knowledge. The reason why it had fallen into disuse probably was that some of the antiseptic substances used for dressing wounds in the Middle Ages were irritants as well as antiseptics. Those who employed them did not know the reason why they were beneficial, and supposed that their virtue was due to their irritating properties. The ointments were accordingly made more and more irritating: and thus more harm than good was done, until they were discarded by Ambrose Paré. The antiseptic most commonly employed is carbolic acid. Not only are all the instruments to be employed disinfected by a watery solution, but the operation itself is conducted under a spray of the dilute acid, so as to render innocuous any organisms which may be present in the air. The wound is then covered with an antiseptic dressing. Whenever this requires to be removed it must always be done under the spray. The reason of these great precautions is obvious: if any germs, however few, gain an entrance they will soon multiply and prove as deadly as a great number, the only difference being one of time.

The great danger which may arise from an exceedingly minute portion of septic matter renders great caution necessary on the part of those who might, by a little indiscretion, convey it from one to another. Thus a number of years ago a medical man was nearly driven mad by an epidemic of puerperal fever which he had in his practice: one patient dying after the other. In order to get rid of any infection, he burnt all his clothes and went away for three months. During his absence everything

went well. On his return the epidemic again broke out: on careful investigation he found the only thing he had forgotten to burn was his gloves, and these had acted as a reservoir of infection. The hands, imperfectly cleansed in the first instance, had conveyed the septic matter into the gloves, and there it remained, re-infecting the hands every time the gloves were put on. In the same way a thermometer may prove a cause of continual infection unless the thermometer be carefully washed, and, if necessary, disinfected, each time it is used and before it is put into the case. In a similar manner it has been found that gonorrhœal matter may remain in the vagina and infect several persons without the woman herself ever suffering. One of the best antiseptics for disinfection in such cases is permanganate of potassium. This may be used to wash out abscesses, if there is any fear of danger from absorption of carbolic acid; and also as a lotion for ulcers or wounds about the mouth, the urethra, or anus, where the carbolic acid might be too irritating; as is evident from Koch's experiment, however (*vide* p. 92), a solution of the strength ordinarily used—one per cent., i.e. four grains to the ounce—is not sufficient to destroy the septic organism, although one of five times the strength will do so.

Another way in which septic poisoning may be produced is by the introduction of a catheter into the bladder, where this cannot be completely emptied naturally on account either of paralysis, enlarged prostate, or stricture. So long as the contents of the bladder have not come in contact with any foreign matter they may remain in the bladder for some time without undergoing decomposition, but if a dirty catheter should be passed, and thus a few organisms introduced into the bladder, decomposition may set up in the urine and septic poisoning ensue. A solution of carbolic acid in oil is sometimes trusted to for the disinfection of catheters, but, as Koch's experiments (p. 96) show that such a solution has little or no antiseptic power, the catheters should be disinfected by a strong solution of carbolic acid in water, and afterwards oiled before their introduction.

The use of antiseptics **internally** is limited by the resistance of the organism itself, as already mentioned (p. 102). In the stomach antiseptics are used for the purpose of preventing decomposition, and by thus lessening the production of irritating products they diminish irritation of the stomach and arrest vomiting. Those which are chiefly employed for this purpose are creasote, carbolic acid, sulpho-carbolates, salicylic and sulphurous acids. In the intestine antiseptics are useful in arresting putrefaction, and thus preventing the harm caused locally to the intestine by the products of decomposition as well as the injury due to their subsequent reabsorption. They therefore tend to check diarrhœa and dysentery. It is probably to its antiseptic action

that corrosive sublimate owes its curative power in cases of infantile dysentery, and it is not improbable that the beneficial action of calomel is due to a similar action, for it has been found by Wassilieff greatly to retard the decomposition due to low organisms.

The beneficial action of mercurials in such cases may be partly due to their antiseptic power not being as greatly diminished by admixture with fæcal matters as that of other antiseptics. After absorption into the blood, antiseptics are chiefly employed in febrile conditions, in order, if possible, both to lessen the growth of the septic organism and to remove the danger to the individual which the fever itself would occasion. The principal antiseptics used for this purpose are alcohol, eucalyptol, quinine, salicin, salicylic acid, and salicylates. Carbolic acid and creasote can hardly be used, as their action on the organism is too poisonous, but hydroquinone, cresotinic acid, kairin, pyrocatechin, antipyrin, and resorcin are not markedly poisonous, and are antipyretic. They may thus be useful, and antipyrin is now largely employed (*vide* also Antipyretics). Eucalyptol has sometimes appeared to me to be more beneficial in cases of septic poisoning than quinine; at any rate, I have seen patients recover under its use who had not been benefited by quinine.

Disinfectants.—These are generally employed in order to destroy the germs of disease in the excreta of a patient suffering from an infectious disease, or those germs which may be adhering to articles of clothing or to furniture or to the walls of a room in which the patient has been lying. Probably the most efficient and generally applicable to articles of clothing is heat. The heat employed is usually from 230° to 250° F., but as a general rule it should be as hot as the fabrics will bear without injury, and should be continued as long as is necessary to raise the central parts of the articles to be disinfected to the temperature of the chamber in which they are placed. As the presence of **moisture** aids the destructive action of heat upon septic organisms, superheated steam appears to be the best disinfectant under ordinary circumstances. The only disinfectant that seems to be really trustworthy for destroying septic organisms when it is simply washed over them is corrosive sublimate: even in a dilution of one to a thousand it appears to destroy microzymes and their spores by a single application for a few minutes.

Deodorizers.—Deodorizers are mainly strong oxidizing and deoxidizing substances, as chlorine and its oxides, sulphurous acid, nitrous acid, ozone, peroxide of hydrogen, permanganate of potassium. Charcoal, in addition to oxidizing, absorbs and condenses the foul-smelling gas. Those which are most commonly used as deodorizers for the air of rooms are chlorine or its oxides set free from chlorinated lime.

For removing smells from the hands, carbolic acid is to be

preferred to others, and for deodorizing fæcal matters, permanganate of potassium, carbolic acid, or charcoal. A mixture of eight or nine parts calcined dolomite (magnesia and lime) with one or two of peat or wood charcoal is not only an excellent deodorizer, but increases the value of the fæcal matters as manure.

Antiperiodics.

These are remedies which lessen the severity or prevent the return of attacks of certain diseases which tend to recur periodically.

The chief of these are :—

Cinchona bark and its alkaloids :—

Quinine.	Arsenic.
Cinchonine.	Salicylic acid.
Quinidine.	Salicylates.
Cinchonidine.	Salicin.

Bebeeru bark and its alkaloid :—

Bebeerine.	Eucalyptol.

Action.—The mode in which antiperiodics act is not at present definitely ascertained, nor indeed is the pathology of the diseases which they prevent. Remittent fever, however, has been shown to depend upon the presence of a spirillum in the blood, and there is considerable evidence for considering that malarious conditions are connected with the presence of a bacillus. The periodical return of the attacks in such diseases would appear, then, to be associated with the growth of successive crops of these protophytes, and the action of antiperiodics might be explained by supposing that they interfere with the development of these pathogenic organisms.

Uses.—Quinine and cinchona bark are often regarded as almost specific in the various affections due to malarious poisoning, i.e. intermittent fevers, periodic headaches, neuralgias, etc. In tropical remittent fever of malarious origin, quinine is also the best remedy we possess. It must be given in very large doses, however, and is less certainly curative than in intermittent fever. The other cinchona alkaloids have a similar action to quinine, but are not quite so powerful : they, as also quinine, may be used as prophylactics in order to prevent the recurrence of ague in persons travelling through or living in malarious districts as well as for the purpose of curing malarious conditions already present.

Arsenic is sometimes even more powerful than quinine, but as a rule it answers best in malarious conditions which are some-

times known as masked or latent malaria, and which manifest themselves in neuralgia and nervous or digestive disturbance rather than in well-marked ague fits.

Adjuncts.—Emetics and purgatives aid the action of antiperiodics, and sometimes, indeed, can replace them and cure ague without their aid. Antiperiodics rarely succeed if the functions of the liver are disturbed unless they are aided by emetics or purgatives, and especially by cholagogues.

CHAPTER IV.

ACTION OF DRUGS ON INVERTEBRATA.

The study of the action of drugs on invertebrata has not been carried out methodically to any great extent, but it offers a very promising field for investigation, and probably in the course of a few years may yield very valuable results.

Action of Drugs upon Medusæ.

This subject has been worked at, almost exclusively by Romanes [1] and Krukenberg.[2] At present it has little practical bearing, but it promises to be of great service by enabling us to understand better the action of drugs on contractile structures generally, and on the heart in particular.

In medusæ the swimming organ consists of a bell-shaped mass of contractile substance, within which the polyp hangs like the clapper. Around the margin of this bell are a number of ganglia connected with one another by nervous filaments, and forming a peripheral ring.

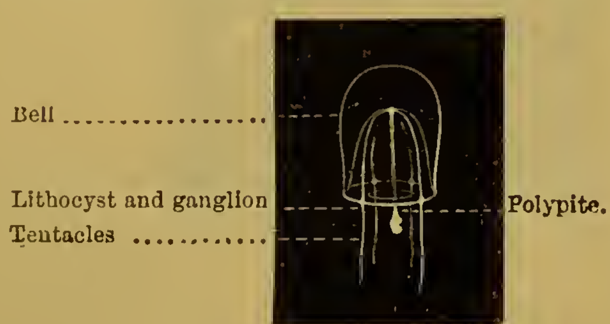

FIG. 29.—Medusa (Sarsia), natural size.

In the normal state of the animal, the bell alternately contracts and dilates rhythmically, so that the animal is propelled through the water.

When the marginal strip containing the ganglia is removed, the bell becomes entirely motionless. The bell thus resembles, as we shall see afterwards, the ventricle of the frog's heart, both in the relation of ganglia to it, and in its rhythmical movements. Oxygen accelerates, and carbonic acid slows and finally stops, the rhythmical movements.

When the bell, paralysed by the removal of the ganglia which supply its normal stimulus to motion, is momentarily stimulated by a single induction shock, it invariably responds by a single contraction.

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[1] Romanes, *Phil. Trans.* vol. clxvi. part 1, and vol. clxvii. part 2, 1866 and 1867.
[2] Krukenberg, *Vergleichend. physiologische Studien*, Heidelberg, 1880.

When successive shocks are employed at regular intervals the effect of each increases until the maximum is reached (Fig. 30, cf. pp. 122 and 123).

FIG. 30.—Shows the increasing contractions of the tissue of the medusa when stimulated by repeated weak induction shocks of the same intensity. The first two shocks had no apparent effect, and the first feeble contraction seen in the figure was caused by the third shock. (From a paper by Romanes in *Phil. Trans.*)

But if an additional **constant stimulus** is supplied to it by the addition of acid to the water in which it is floating; by the passage of a constant or of an interrupted electrical current through it; or by alcohol or glycerine dropped upon its surface, it commences to beat regularly, rhythmically, and continuously. When rhythmical action is thus artificially induced in the paralysed bell, its rate is increased by raising the **temperature,** and reduced by cooling it. Temperatures below 20° or above 85° arrest the rhythm.

When the marginal strip containing the ganglia is cut off and left attached only at one point, a stimulus applied to its end travels along the strip and finally causes the bell to contract. The **stimuli** which pass along may be

Strip of contractile tissue with fringe of tentacles..........

FIG. 31.—Diagram of a medusa (tiaropsis), about one-third natural size, with a strip of contractile tissue cut from the bell, but left attached at one end.

of two kinds—they may occur separately or together. The first kind is a wave of contraction in the **contractile tissue** of the strip itself. If the stimulus is applied to a portion of the strip the contraction will pass along like a wave until it reaches the bell, which it excites to contraction. The second is a rudimentary form of **nervous** activity. This may occur along with the contraction wave, and when this is the case it is seen to pass along in front of the contractile wave. But it may also occur when no wave of contraction takes place. Its occurrence is rendered visible by the movements of the tentacles which fringe the strip and are much more sensitive than the contractile tissue of the strip itself. This wave of stimulation without contraction passing along the strip will cause the bell to contract on reaching it, provided there is a marginal ganglion in the bell, but not if the bell is paralysed. The wave of stimulation is more easily excited than that of contraction, so that it may occur from stimuli too weak to excite a wave of contraction. The passage of stimuli along the strip may be impeded or prevented altogether by compressing the strip, by making transverse incisions into it so as to narrow the band of tissue by which the wave is transmitted, or by injuring the tissue

by straining. Sometimes the contraction wave may be **blocked** by the injury before the stimulus wave, and sometimes the stimulus wave may be blocked before the contraction wave. When the block is only partial it frequently happens that two or three waves will pass along the strip up to the block without being able to cross it, but after a long time their effect appears to penetrate so that a wave at last crosses it.

As Gaskell has shown, a similar occurrence takes place in the frog's heart, and stimuli proceeding from the auricle to the ventricle may also be blocked by compression.

The influence of **poisons** can be studied either upon the bell containing the ganglia, or upon this marginal strip.

In healthy medusæ chloroform first arrests the spontaneous movements of the bell. When now irritated it answers by a single contraction, instead of by a series, to such stimulation.

After the bell has ceased to respond, nipping its margin causes the polyp to contract.

After stimulation of any part of the bell ceases to produce response in any part of the organism, the polyp will respond to stimuli directly applied to it. Nitrite of amyl also produces effects which in many respects are similar to those of chloroform. There are, however, certain exceptions; the first is that, before the spontaneous movements are abolished, the rhythm becomes quickened, and the strength of the pulsations is diminished. The movements also die out more gradually than under chloroform, and before they entirely cease they become localised to the muscular tissue close to the margin. When the dose is large, spasmodic contractions are produced which obliterate the gradual paralysing action of the drug.

Caffeine first causes an increase in the rate of pulsation, and diminishes its strength after a few seconds. This condition passes off, and the spontaneous movements become gradually abolished. They still remain for a long time sensitive to stimulation, and at first respond by *several* feeble contractions to each stimulus; afterwards by a single response; and afterwards they do not respond at all.

As medusæ paralysed by removal of the ganglia never respond to a single stimulus with more than a single contraction, the increased number of contractions which at first appear after the application of the stimulus, are probably due to increased reflex irritability.

Caffeine causes the tentacles and polypi to lose their tonus, and become relaxed, which is not the case with chloroform. Medusæ anæsthetised with chloroform when put into a solution of caffeine also lose their tonus, but their irritability is restored, though their spontaneity is not.

The effects of strychnine differ in different species of medusæ. In Sarsia it accelerates the rhythmical contractions which occur in groups separated by intervals of quiescence. This quiescence finally becomes continuous, and during it the animal does not respond to irritation of the tentacle, but does so to direct muscular stimulation.

Veratrine first increases the number and power of the contractions; afterwards it diminishes both.

Digitalin first quickens them, then renders them regular, causes persistent spasms, and produces death in strong systole.

Atropine causes first acceleration, then convulsions, then feeble contractions, and finally death in systole.

Nicotine causes violent and continuous spasm, with numerous minute rapid contractions superimposed upon it. These latter soon die away, leaving the bell in strong systole.

After spontaneous movements have disappeared, the bell no longer responds to stimulation of the tentacles, but responds to direct stimulation.

Alcohol first greatly increases the rapidity of the contractions, so much so that the bell has no time to expand properly between them, and they are in consequence feeble and gradually die out. The reflex stimulation shortly ceases to produce any effect, but muscular irritability is longer maintained.

Cyanide of potassium first quickens and then enfeebles the contractions; spontaneous movements rapidly cease, and the bell soon becomes irresponsive either to irritation of the tentacles, or to direct irritation. For a long time after it has become irresponsive, the nervous connections between the tentacles and polyp remain intact, as also do the nervous connections of these organs with all parts of the bell. The sensory organs are therefore not paralysed by this drug.

The effects of poisons on medusæ were localised by Romanes in two ways. One way was to divide the medusa almost into two halves, connected only by a narrow strip of tissue. These halves were plunged into two beakers filled with sea-water, pure in one and poisoned in the other. The connecting strip

FIG. 32.—Diagrammatic representation of the method of localising the action of poisons on medusæ. One vessel contains normal sea-water; another contains poisoned sea-water, which is shaded in order to distinguish it.

rested upon the edges of the beaker. When curare was employed as a poison in this way, it was found to have an action similar to that which it exerts on mammals: apparently paralysing the motor nerves, while it left the sensory nerves capable of action. Thus, on nipping the half of a medusa which was plunged in the curare solution, it remained absolutely motionless, while the other half at once responded by a peculiar contraction to the stimulus. Here, also, however, just as in mammals, the sensory fibres are also paralysed by a large dose, so that if much poison be used, irritation of the poisoned part will have no effect either upon it or upon the unpoisoned part. When experimenting in this way with strychnine, Krukenberg found that the excitability of the poisoned part was increased, so that when he touched the connecting strip lightly with a needle no effect was produced on the unpoisoned half, but the poisoned half responded by several energetic contractions. Veratrine had a similar action to that of curare, so that irritation of the poisoned half caused no movement in it, but caused movement in the unpoisoned half. The irritability of the contractile tissue is also diminished so that it no longer reacts so readily in the poisoned half to electrical stimuli.

Nicotine appears to paralyse the ganglionic structures and not the nerves.

It has already been mentioned that the rhythmical movements of medusæ depend upon the ganglia: when these are all cut off the movements cease, but if only one be left the movements continue. In the medusa divided into two halves, as already described, it is evident that if the ganglia are removed from one half, or one half rendered functionally inactive by poison, that half will still continue to contract, so long as it remains connected with the other half, but will cease to move when it is completely divided from the half which still contains ganglia. The effect of nicotine is such as one would expect if the poison paralyses the ganglia, for it is found that when one half of a medusa is steeped in water containing nicotine, both halves still continue to pulsate rhythmically; so soon as the connecting band of tissue is divided, the poisoned half at once ceases to move, while the other half continues to pulsate.

The second way in which Romanes localised the action of poisons on medusæ was by applying them to a strip of contractile tissue. He found that various poisons applied to the strip, or injected into it, caused a blockage of contractile waves, preceded by a progressive slowing of the rate of transmission along the poisoned part. Chloroform, ether, alcohol, morphine, strychnine, and curare, all have this effect.

General Results.—The most marked results of experiments on medusæ are, that the contractile tissue **contracts rhythmically** when stimulated by ganglia. It ceases to do so when the ganglia are removed and the contractile tissue left under ordinary conditions, but a constant stimulus, either chemical or electrical, applied to it after the removal of the ganglia, will cause it to beat rhythmically just as if the ganglia were present. This appears to show that the rhythmical contractile power is a function of the contractile tissue and not merely of the ganglia. Besides its power of contracting once on the application of a single stimulus, or rhythmically from continued stimulation, the contractile tissue also possesses the power to **conduct** stimuli. This is seen in the passage of the contraction wave along a strip of medusa which, on reaching the bell, causes it to contract. When two contraction waves travelling along the contractile strip in opposite directions meet one another they arrest each other. This mutual extinction may be regarded either as a process of **inhibition** or interference, or as a consequence of exhaustion of the tissue which possibly may be unable to contract twice with such a short interval between.

The power of the contractile tissue to transmit stimuli is diminished or destroyed by cutting it more or less completely across, by compression, by stretching, by very high or low temperatures, and by poisons such as chloroform, morphine, nitrite of amyl, caffeine, strychnine, curare, and indeed almost any foreign substance added to the water in which the strip is immersed.

There are, however, **two conducting channels**, along which stimuli may be transmitted; the first, already mentioned, is the **contractile tissue**; the second is the **nervous tissue**. The passage of stimuli along the second is rendered evident by the movements of the tentacles. These nervous or tentacular waves and the contractile waves may exist either together or separately. The nervous waves are excited by stimuli which are too weak to excite contraction waves, and it is to be particularly remarked that when this is the case they only travel at half the rate at which a contraction wave travels, although, when the stimulus is strong enough to excite a contraction wave also, both the nervous and the contractile wave travel at the same rate, the nervous one being a little ahead of the other. The passage of nervous stimuli may also be diminished or completely blocked by section or compression just as in the case of contraction waves.

The transmission of stimuli along nerves is also affected by poisons. It appears to be destroyed by anæsthetics, though more slowly than that of the contractile tissue. The ganglia may be paralysed, e.g. by nicotine, before the transmission of nervous stimuli from them is diminished. The contractile tissue alone may be paralysed.

Action of Drugs on Mollusca.

In the **lamellibranchiata,** instead of a chain of ganglia, as in the medusæ, we have three pairs of ganglia: cerebral at the mouth, pedal in the foot, and parietal-splanchnic supplying the bronchial apparatus and viscera. The heart has distinct chambers, but apparently consists of protoplasmic substance without distinct nerves or ganglia. The application to it of an interrupted current will arrest the rhythmical pulsation and cause stoppage in diastole.[1] This effect is prevented by atropine. Warmth up to 104° quickens the heart; when raised higher it destroys reflex movement in the animal, and afterwards arrests the heart also. Pure water without salts quickly paralyses the muscles and causes death in salt-water molluscs. Curare in small doses has no effect, large doses quicken, but do not abolish movement, and do not affect the heart. Strychnine somewhat stimulates movement, and may cause some local contractions, but never any general tetanus. Nicotine acts in a similar way, but in large doses appears to paralyse the muscles and cause death; it also appears to cause contraction of the vessels, so that the heart becomes more bulky and beats more quickly. Veratrine has a similar action. Digitalis has no action, excepting when applied to the heart directly, and then it renders the beats slower and sometimes stops them. Antiarine, like digitalis, has no general action, but stops the heart if applied to it directly. Muscarine generally causes muscular contractions in the body: first acceleration, quickly followed by retardation of the cardiac beats. Sulphocyanide of potassium diminishes reflex action, but has little effect on the excitability of the nerves. A small dose somewhat quickens the cardiac action; a large dose stops the heart in diastole, and if it is directly applied to the heart the stoppage is permanent.

Action of Drugs on Ascidians.

The heart in ascidians consists of a tube open at both ends, and which, by its contraction, drives the visceral fluid alternately towards the viscera and away from them. Its action does not seem to depend on the nervous ganglion lying between the oral and anal sac, or indeed upon nervous influence at all.

The application of an induced current causes it to beat for some time in one direction instead of alternately, but does not arrest its pulsations.[2] According to Krukenberg it is not affected either by atropine or muscarine. It is paralysed by veratrine, quinine, and strychnine: these poisons rendering the beats gradually weaker and more irregular. No evidences of tetanus are to be seen from the action of strychnine. The mode of action of the heart is affected by helleborin and nicotine: helleborin increases the number of the advisceral beats while nicotine diminishes them. Camphor and strychnine have possibly an action in this respect resembling helleborin.

Action of Drugs on Annulosa.

In annulosa the nervous system consists of ganglia in each segment united together by nervous bundles. These bundles in general appearance correspond with the gangliated cord of the sympathetic in higher animals. The spinal cord is absent: we might therefore expect that drugs which act specially on the spinal cord in vertebrates would not have the same

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[1] M. Foster, Pflüger's *Archiv*, v. 191.
[2] Dew-Smith, *Proc. Roy. Soc.*, March 18, 1875, p. 336.

marked action on annelida, and this appears to be the case. It was found by Moseley that strychnine had no action on cockroaches;[1] and leeches, when placed in water containing strychnine, become elongated but do not exhibit signs of tetanus. Some years ago I noticed that ants sprinkled with insect-powder died in violent convulsions, and it occurred to me that possibly substances which excite movements of the intestine in the higher animals might have a somewhat convulsant action on invertebrates. I therefore tried the effect of oil of peppermint on leeches, and it produced in them violent excitement. This appears to be of a somewhat convulsant nature: the animal at first flying rapidly hither and thither through the water, and afterwards, when it becomes quiet and nearly exhausted, there is a constant rhythmical twitching movement in the body which appears to last nearly until death. But if my idea had been correct, all carminatives should excite convulsions in annulosa. This is not the case, for the oils of peppermint, caraway, and anise have no apparent effect on black-beetles other than that of making them sluggish.

Chloroform, ether, and other substances belonging to the alcohol group, act as anæsthetics on mammals, temporarily abolishing the functional activity of the brain, spinal cord, and medulla. On annulosa they have a similar action, although Krukenberg[2] supposed they had a different effect, coagulating the muscular substance and rendering it stiff and hard before affecting the nerves. The experiment by which he thought this was

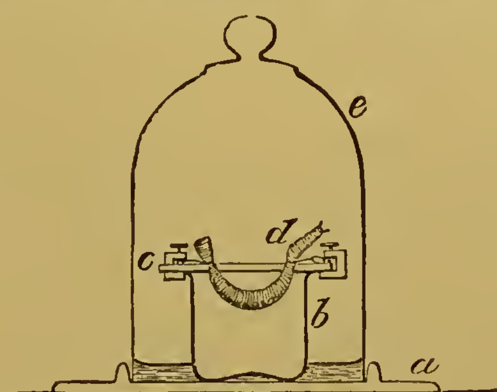

FIG. 33.—Krukenberg's apparatus for investigating the action of chloroform, &c., on annulosa. *a* is a shallow vessel containing a little water. *b* is a beaker containing water, saturated with chloroform, or ether, and covered with a piece of millboard *c*, in which are two holes. Through these holes the head and tail of a leech, *d*, are drawn and fastened by ligatures held by two clamps. *e* is a bell-jar covering the whole.

proved consisted in applying chloroform to the middle part of a leech while the two ends of the animal were protected from the action of the vapour. The middle part then became stiff and rigid, but the movements of the two ends of the animal were perfectly co-ordinated, so that its actions were that of a single animal having a stiff girdle surrounding its middle. Ether and alcohol had a similar result. The co-ordination of the two ends showed that although the muscles had been rendered rigid by chloroform, the nerves which passed through the middle part of the body were still functionally active. When the middle part of the body was coagulated by the application of hot water, the muscles became rigid but the nerves were also destroyed, and the movements of the two ends of the animal were no longer co-ordinated, so that they appeared like two distinct animals connected by a rigid cylinder. Luchsinger[3] repeated Krukenberg's experiments, and found that although the muscles were affected by the chloroform, yet the nervous system was still more sensitive than the muscles.

[1] Moseley, unpublished experiment made in C. Ludwig's laboratory.
[2] Krukenberg, *Vergleichend. physiologische Studien*, Abtg. I., p. 77.
[3] Luchsinger *und* Guillebeau, *Pflüger's Archiv*, xxviii., p. 61.

Atropine has a similar action to chloroform, ether, and alcohol, on the muscles of the leech. Veratrine appears to some extent to affect the muscles, so that after contraction they relax slowly. It appears also, however, to affect the nerve-centres, and, according to Krukenberg, paralyses more especially the sensory centres. Camphor, strychnine, morphine, caffeine, copper sulphate, and mercuric chloride act chiefly on the nervous system of leeches, although they also affect the muscles when applied for a length of time. Caffeine renders the muscles in the leech also rigid.

CHAPTER V.

ACTION OF DRUGS ON MUSCLE.

Action of Drugs on Voluntary Muscle.

In the bodies of animals we find the protoplasmic masses or cells of which they are composed variously modified, in order to perform special functions.

In some the power of nutrition is chiefly developed: and this we find in glands. In others the power of contractility is developed: and this we find in muscles, striated and non-striated.

In the course of special development towards the fulfilment of a particular function, the protoplasm of the muscular cells undergoes marked changes. But it must always be borne in mind that the protoplasmic elements of the body, however different from one another, always tend more or less to retain all the functions which are seen in an organism consisting of a single cell, a reference to which may sometimes throw much light upon the mode of life of the more highly organised tissues.

In amœbæ or leucocytes the protoplasm contracts in any direction and when strongly contracted in tetanus they become spherical.

In muscle the protoplasm is specially modified and contracts chiefly in one direction, viz. that of its length, and, indeed, it is usually assumed that muscular fibre, either voluntary or involuntary, contracts in the direction of its length only.

But the probability of its contraction in a transverse direction also is to be borne in mind, and there are some phenomena which it is very hard to explain except on the *supposition that muscle contracts transversely as well as longitudinally.*[1]

We distinguish in muscle its **elasticity**, a physical property; and its **contractility**, a vital property.

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[1] Thus Weber found that when a muscle is loaded with a weight too great for it to lift, instead of shortening, it elongates. The usual explanation of this is that the elasticity of the muscle then becomes diminished; but according to Wundt the elasticity is not changed. If we suppose that stimulation tends to make the muscle contract transversely as well as longitudinally, the explanation is easy, for in this case, longitudinal contraction being prevented, the transverse contraction tends to elongate the muscle.

The word elasticity is applied to the tendency of the body both to resist change of its form, and to regain it when this change has been effected: so that ivory may be taken as the type of a very strongly elastic body. Indiarubber, on the other hand, is regarded as a feebly elastic body, because it does not strongly resist changes of form, although it tends very strongly to regain its original form after such changes. It is, however, popularly regarded as the perfect type of an elastic body. In talking of the elasticity of muscle, confusion is apt to occur; it is better, then, to avoid the term elasticity and to use the words suggested by Marey—extensibility and retractility. The **extensibility** of muscle is of two kinds—immediate and supplementary. When a weight is attached to it, it extends considerably; this is its immediate extensibility; it then goes on slowly and gradually lengthening for a considerable time, and this is supplementary extensibility. When the weight is removed the retractile power of the muscle again becomes evident, and there is immediate **retractility** and supplementary retractility, the muscle at once contracting to a considerable extent, and then continuing to do so slowly and gradually for some time afterwards.

The extensibility of a muscle is increased by stimulation, so that if a weight be hung on a muscle while it is contracted in consequence of stimulation, it will produce a greater extension than it would if applied to the same muscle in a state of rest; and if a muscle be loaded with a weight too great for it to raise, stimulation, instead of causing contraction, causes elongation.[1] Heat renders the muscle less extensible and more retractile; cold has an opposite effect, rendering it more extensible and less

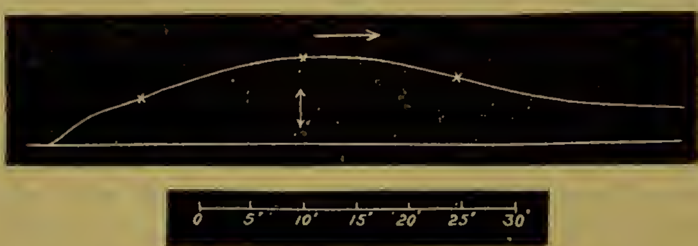

FIG. 34.—Shows the action on muscle of caustic soda, 1 in 2,500, once renewed in 25 minutes, followed by the action of lactic acid, 1 in 500, once renewed in 25 minutes. (Brunton and Cash.)

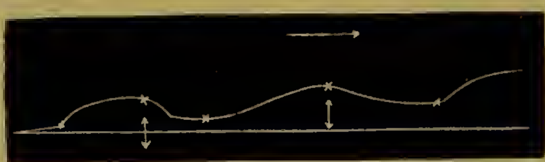

FIG. 35.—Shows the action on muscle of caustic potash, 1 in 2,500, twice renewed for 13 minutes, succeeded by the action of lactic acid, 1 in 500, for 18 minutes, and this by the action of caustic potash for 17·5 minutes. (Cf. Fig. 50, p. 132.) (Brunton and Cash.)

retractile. Section of the nerve has a similar effect to that of cold. Fatigue increases the extensibility. Alkalis (potash or

[1] *Vide* footnote, p. 117.

soda), in very dilute solutions, diminish extensibility; dilute acids (lactic acid) increase it. By the alternate application of

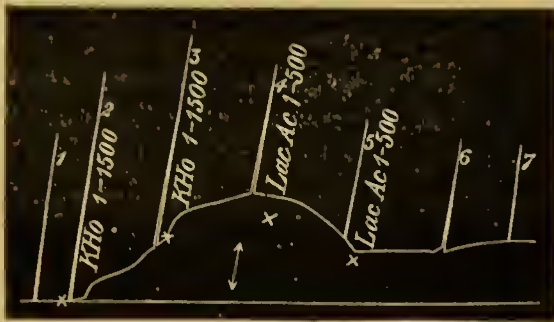

FIG. 36.—Shows the action of caustic potash, 1 in 1,500, on muscle for 18 minutes, succeeded by the action of lactic acid for 24 minutes. 1 is the contraction of normal muscle; 2, 3, 4, contractions of alkali-muscle; 5, 6, 7, contractions of acid-muscle on stimulation. (Brunton and Cash.)

alkalis and acids the muscle may be made to yield curves which, when recorded on a very slowly-revolving cylinder, are similar in form to the normal contraction curve recorded on a rapidly-revolving cylinder.[1] Fig. 34.

Irritability of Muscle.—In order to ascertain the irritability of muscle itself or the readiness with which it responds to various stimuli independently of the nerves within it, the muscle is first poisoned by curare, and then exposed to various conditions, or to the action of drugs. The muscle thus poisoned by curare, woorara, woorali, or urari (for the poison has all these names), is much less sensitive to the action of faradaic currents. The readiest way of testing its excitability is by the making and breaking of a constant current, the strength of which can be estimated very exactly by using du Bois Reymond's rheochord. The excitability of muscles is **increased** by heat and **diminished** by cold. It is increased by physostigmine and diminished by most poisons which paralyse muscle.[2]

Contraction.—When the ends of the muscle are not kept apart by force too great for it to overcome, and it is stimulated by heat, mechanical injury, chemical irritants, or electricity, it contracts and then relaxes.

The form of this contraction varies according to the species of animal, and the particular muscle tested.

In cold-blooded animals, as a rule, the contraction is slower than in warm-blooded animals. It is not alike in all the muscles of the body of mammals. Thus in the rabbit there are two kinds of muscles—red and white; the white muscles contract more quickly and relax more quickly than the red ones. The muscle usually employed in experiments is the gastrocnemius of the frog, freshly prepared, with the nerve and end of the femur attached to it.

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[1] Brunton and Cash, *Phil. Trans.*, 1884, p. 197.
[2] Harnack and Witkowski, *Arch. f. exp. Path. u. Pharm.* v. 1876, p. 402.

The femur is fixed in a clamp, and the lower end of the muscle is attached to a writing lever usually loaded with a weight (Fig. 37). The end of this lever writes upon a revolving

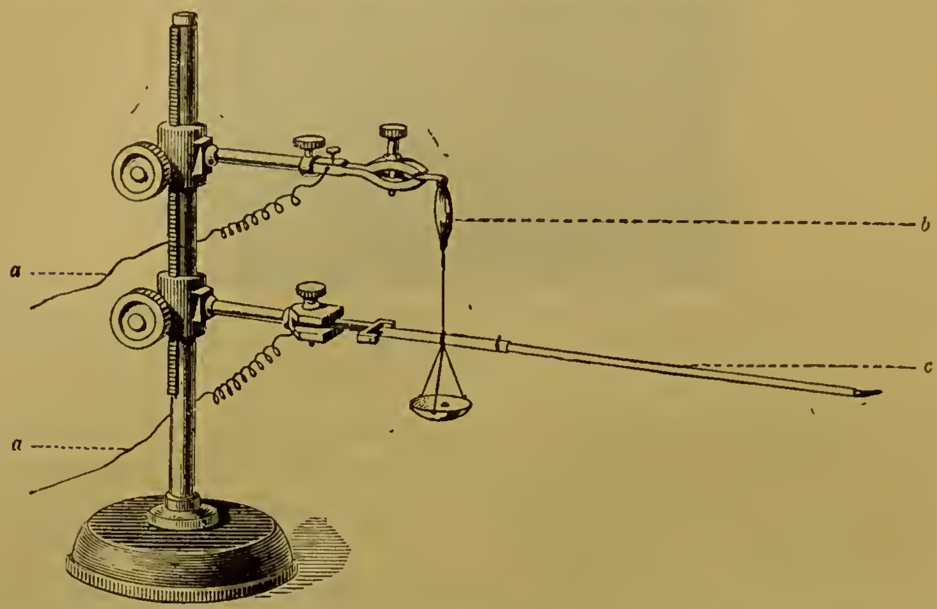

FIG. 37.—Apparatus for registering muscular contraction. It consists of an upright stand on which two horizontal bars may be moved by a rack and pinion. The upper bar ends in a clamp, the lower carries a delicate lever, the part near the hinge being of metal, and the part beyond of light wood tipped with quill or tinfoil. *a*, *a*, wires for exciting muscle; *b*, muscle; *c*, writing lever. In the figure no arrangement is shown for exciting the nerve, and for the sake of simplicity the weight is shown directly under the muscle. In actual experiment, however, the weight should be applied close to the axle, or on it, so as to lessen oscillation due to the inertia of the lever.

cylinder (Fig. 38), which is made to rotate with greater or less rapidity. The rate of revolution is usually ascertained by marking the time upon it by means of an electro-magnet (Fig. 39) communicating with a clock or metronome, or, when the revolution is quick, with a large tuning-fork vibrating 100 times or more per second. When the cylinder is not in motion each contraction of the lever makes a straight line upon it (Figs. 40 *a* and 46); when the cylinder is moving, the lever describes a curve which is more or less elongated, according to the rapidity of the cylinder's rotation (Figs. 40 and 41).

Latent Period of the Muscle.—The mechanical energy developed by muscle during its contraction is derived from chemical energy liberated by changes in the constituents of the muscle itself. These are of the nature of oxidation, and during them oxygen is used up, and carbonic acid is liberated. But the oxygen is not necessarily present either around the muscle, or in the blood circulating through the muscle; it is stored up in some loose form of combination within the muscle.[1]

[1] It would appear that this force-yielding substance, or muscle-dynamite, as we may call it, is not present, at least in large quantity, in the muscles in a form in which it can be at once fired off. There appears rather to exist a substance yielding it, or dynamogen, which may be looked upon as corresponding to the zymogen of the glands, while the muscle-dynamite may be regarded as corresponding to the ferments of glands. Irritation of a nerve appears both to liberate muscle-dynamite

The form in which it is stored up has been compared by Ludwig to gunpowder, a small quantity of which is fired off at each contraction.

One of the final products is carbonic acid; but there are intermediate products, one of them being sarcolactic acid; and these products tend to cause muscular fatigue.

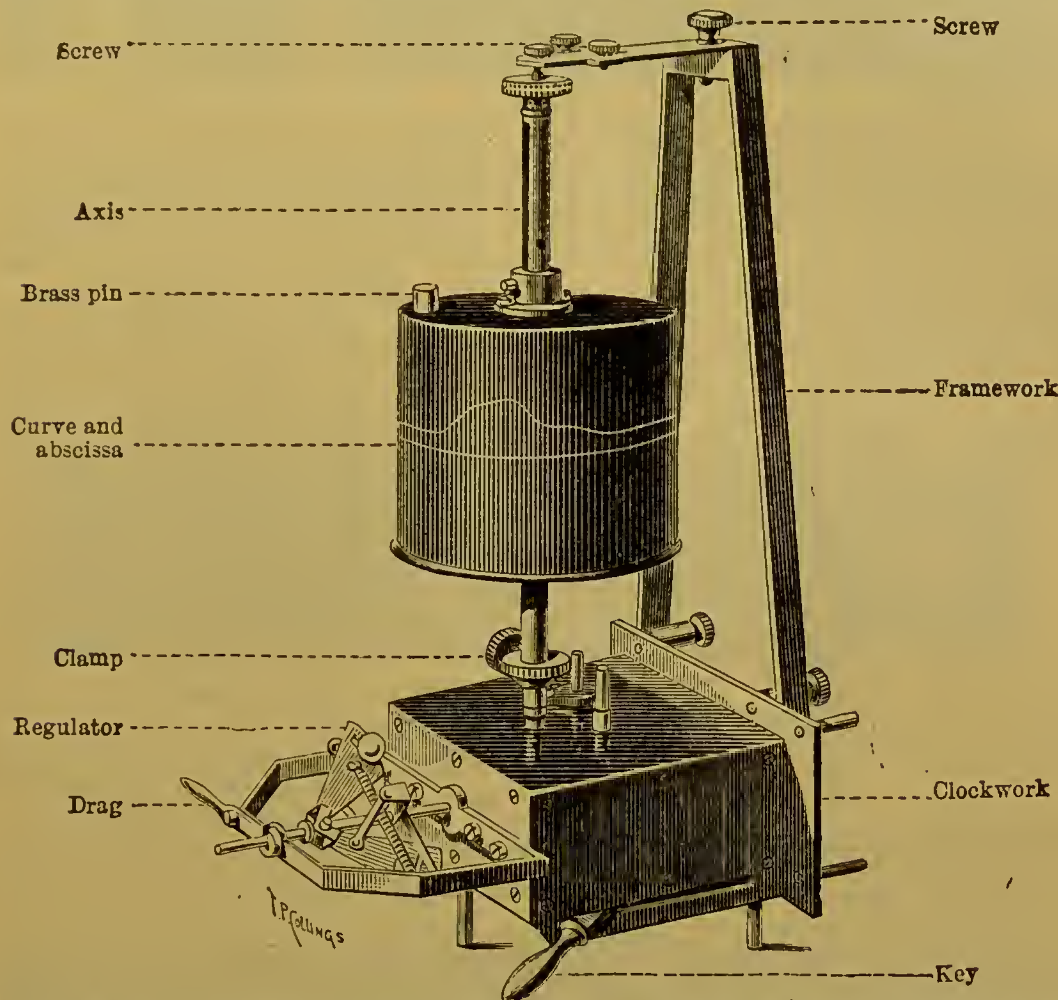

FIG. 38.—Revolving cylinder for recording movements. The screws at the top are for fixing the cylinder in position. The brass pin is for making or breaking a current at a given time in the revolution. It does this by striking against a small key. The curve is described by the lever, Fig. 37. The abscissa, or zero line, is drawn by a fixed point, and serves to show the height of the contraction.

When they are washed out of the muscle by a current of blood, or of simple saline solution, the fatigue of the muscle is removed; and this removal is effected even more perfectly when the internal oxidation is rendered more complete by adding permanganate of potassium to the solution, or by the addition of minute quantities of potash. A mere trace of veratrine has also a similar effect in restoring the muscle after fatigue.

and to explode it, if we may so term it. The passage of a constant current through the muscle appears to liberate the muscle-dynamite from the dynamogen, but causes no expulsion except at the moment when the current is made or broken, or its strength altered. It must be carefully borne in mind that the idea of a muscle-dynamogen is at present simply theoretical, and must be looked upon not as a fact but rather as a means of remembering facts. According to A. Schmidt, however, the contraction and relaxation of muscle is closely connected with the formation and destruction of a ferment.

We find that the muscle does not immediately respond to a stimulus, but that a period elapses between the stimulus and the commencement of the contraction, which is on the average about the 100th of a second. This is termed the **latent period.**

During this period a chemical change is probably going on in the muscle, and it is evidenced by an electrical change known as the negative variation, or diminution in the natural current which passes from the longitudinal to the transverse section of the muscle.

The latent period is altered by fatigue. Loading the muscle shortens the latent period, until the load is just sufficient to extend the muscle. An increase of load above this, lengthens the latent period. Cold lengthens it; heat shortens it. Small doses of strychnine or veratrine shorten the latent period. Large doses of strychnine or veratrine, and also curare, lengthen it.

Summation of Stimuli.—During the latent period, the stimulus applied to a muscle excites chemical changes which result in contraction; but if the stimulus be very small, the

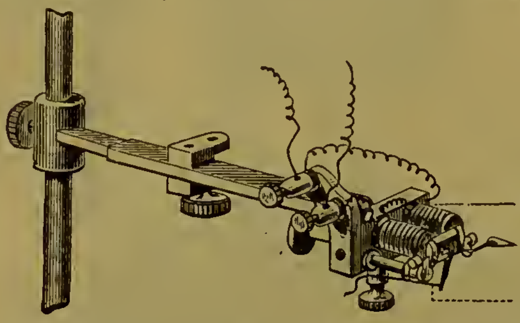

FIG. 39.—Electro-magnet (after Marey) for recording time on a cylinder. When used to record time, the current is made and broken alternately by clockwork or by a tuning-fork. It may be used also to record the time of irritating or dividing a nerve, or of injecting a poison, &c.

chemical changes may be so slight that contraction does not occur. If the stimulus, however, be repeated several times, the changes which it induces in the muscle become sufficient to produce at first a slight contraction, and then one greater and greater, until the maximum effect is produced—this is called **summation.** It occurs not only in voluntary muscles, but in other contractile tissues, such as those of the medusa (*vide* Fig. 30, p. 110). A similar phenomenon occurs also in the heart, and has there received the name of 'the staircase.'

Contraction of Muscle.—In the muscular curve we notice (1) the rapidity of its rise, which indicates the rapidity of contraction of the muscle; (2) its length, indicating the duration of contraction; (3) its height, indicating power of contraction; and (4) slowness of fall, indicating the condition of extensibility.

The muscular contraction is modified by numerous conditions.

One of these is the **strength of stimulus.**

The stimulus usually applied is electricity, as its strength can be more easily regulated, and it does not destroy the muscle so readily as mechanical or chemical irritants.

With a weak current, making (closing) has no action on the muscle, but breaking (opening) causes contraction.

FIG. 40.—Muscle curves, showing the different appearances they present according to the rate at which the recording cylinder revolves. *a* is a curve with a very slowly revolving cylinder; *b*, *c*, and *d* are curves with increasing speed of rotation. *c* is written with a lever pointing in the opposite direction from that with which *a* and *b* are recorded, and the curve therefore inclines to the other side.

A moderate current gives contraction both in making and breaking, but that of making is comparatively small (Fig. 41). With a strong current no difference is observed.

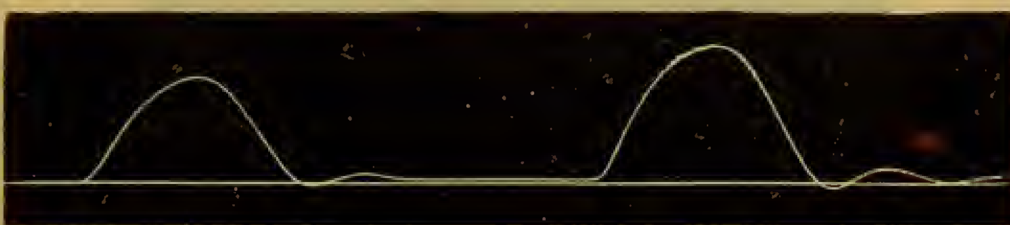

FIG. 41.—Shows effect of making and breaking shocks. These are normal muscle curves with a still quicker rotating cylinder than in Fig. 40*d*. The first is caused by irritating the muscle by making (closing) a constant current, and the second by breaking (opening) it.

The more intense the stimulus, the higher and longer is the curve. The increase in height is shown in Fig. 42.

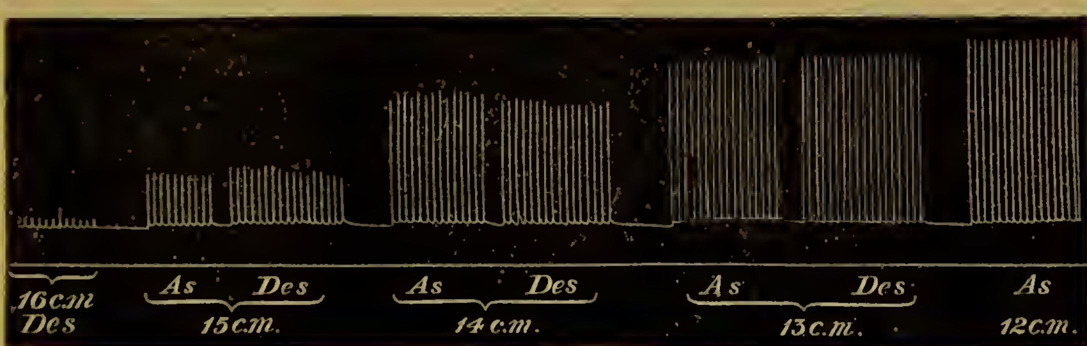

FIG. 42.—Tracing of the contractions of a muscle with stimuli of varying strength. The numbers indicate the distance in centimetres of the secondary from the primary coil in the induction apparatus. *As* and *Des* indicate the ascending and descending direction of the current.

Cold renders contraction slower, lower, and more prolonged (Fig. 43 *b*).

Heat renders it quicker, higher, and shorter (Fig. 43 *a*).

Fatigue.—Fatigue makes the ascent slow, the height less, and the descent slow (Fig. 44).

Exhaustion of the animal has a similar action; and dilute acids applied to the muscle produce the same effect (Fig. 36).

The effect of fatigue is probably due in a considerable measure to the accumulation of acid products of muscular waste.

a b

FIG. 43.—Effect of heat and cold. In *a* the muscle has been artificially warmed, and in *b* it has been cooled.

When these are washed out by passing a weak solution of chloride of sodium through the vessels of the muscle, or partially removed by kneading, it regains to a great extent its normal power of contraction.

FIG. 44.—Effect of fatigue.

Oxidising agents, such as permanganate of potassium, added to the salt solution, increase its power, and restore the muscle even more quickly and completely.[1]

Deprivation of blood has a similar action on the muscle to fatigue; and free circulation of blood tends to remove the effects of fatigue.

Contracture.—When the stimulation is exceedingly strong, the relaxation after contraction may become very slow, and the descent of the curve may be divided into two parts. At first it descends for a short time pretty quickly, and then falls very slowly indeed. This long contraction of the muscle is known as **contracture.** It is very strongly marked in muscles poisoned by veratrine or barium. It occurs, though to a less extent, in muscles poisoned by salts of calcium and strontium, by ammonia, and by the chloride, iodide, nitrite, nitrate, and cyanide of ammonium.[2]

The cause of contracture is not known; it is considered not to be a tetanic contraction, because unlike an ordinary tetanised muscle it does not give rise to secondary tetanus in another frog's muscle, when the nerve of the latter is placed upon it. It is, however, an active contraction, not a mere alteration in the elasticity of the muscle preventing its relaxation; for, as Fick and Boehm have shown, a much greater amount of heat is

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[1] Kronecker, Ludwig's *Arbeiten*, 1871, p. 183.
[2] Brunton and Cash, *Proc. Roy. Soc.*, 1883.

developed during the long-continued contracture than in an ordinary contraction. Sometimes, and indeed not unfrequently, the contracture, instead of consisting of a single prolonged contraction, appears in the form of a prolonged contraction added on to an ordinary contraction before relaxation has had time to occur. This gives rise to a peculiar hump in the curve, as is well seen in the middle curve in Fig. 49. This appears to show that the contracture is really a double phenomenon, like the two contractions observed after a single stimulation in the muscle of

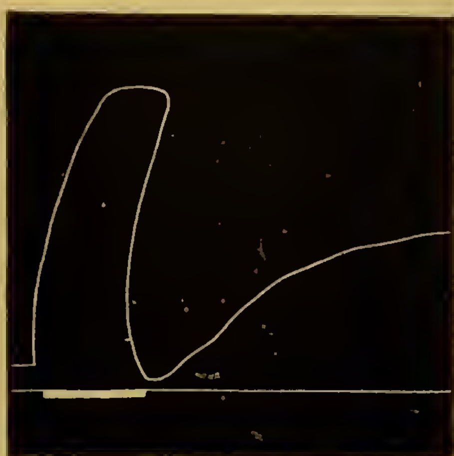

FIG. 45.—Secondary contraction in the muscle of a crayfish. The thick part of the lower line shows the time during which the muscle was irritated by a tetanising current. It will be noticed that the secondary contraction occurs after the irritation has ceased, and after the tetanus caused by it has relaxed. It is not a simple continuous rise, but exhibits several waves indicative of a kind of rhythm. (After Richet.)

the crayfish by Richet (Fig. 45). How far the contracture may depend upon irritation of the muscle by its own current has yet to be determined.

Tetanus.—If instead of a single stimulation a number of stimuli rapidly succeeding each other are applied either directly to the muscle itself or to its motor nerve, we get, in place of a single contraction, a continued contraction or tetanus. As this is due to a fresh contraction of the muscle occurring before the previous one has had time to relax, it is evident that the number of stimuli requisite to produce this will vary with the length of each single contraction in a muscle. Thus in the muscles of the tortoise, which contract and relax very slowly, tetanus may be produced by 3 stimuli per second, while in the white muscles of rabbits 20 may be necessary, and in some muscles of birds 70 stimuli per second are insufficient. It has been said that with as rapid stimuli as 250 per second the tetanus ceases, and after a single initial contraction a muscle goes to rest just as if a constant instead of an interrupted current had been used. Kronecker and Stirling have shown that, with no less than 22,000 interruptions per second, tetanus is still obtained; but when such extremely rapid stimuli are applied, the muscle still contracts about the ordinary rate of 20 per second; and this is also the

case when chemical stimuli are applied to the nerve, or when the muscle is irritated by the nerve-centres, either voluntarily or by artificial stimuli applied to them. It seems therefore probable that the number of contractions of the muscles in tetanus are not due to the number of stimuli sent down from the nerve centres, but that the rate is determined either by the ends of the nerve in the muscle or by the muscle itself.[1]

The form of a tetanus curve may be modified very considerably by the action of drugs: thus substances which diminish the contractile power of muscle cause the tetanus curve to fall very rapidly notwithstanding the continued application of stimuli either to the muscle itself or to its nerve (*vide* Ammonia).

Muscular Poisons.—We may distinguish several groups of muscular poisons, but at present the classification is difficult, and the division into six groups based on that of Kobert, which I have adopted, although it possesses some advantages, is far from satisfactory, and can only be regarded as temporary.

GROUP I.—Leaves the irritability of the muscle unaffected, but diminishes the total amount of work it is able to do.
GROUP II.—Diminishes the excitability of the muscle as well as its capacity for work.
GROUP III.—Diminishes the capacity for work, and produces marked irregularity in its excitability.
GROUP IV.—Alters the form of the muscular curve.
GROUP V.—Increases the excitability.
GROUP VI.—Increases the capacity for work.

FIG. 46.—Tracings showing the gradual loss of contractile power from fatigue in a normal muscle, *a*, and in one poisoned by carbolic acid, *b*. Each section, 0'—1', &c., shows the contractions in one minute. (After Gies.)

The poisons in Group I. do not alter the muscle curve, so that if the action of the poison were tested by a single contraction only, it would be supposed that the muscle was unaffected; they lessen, however, the amount of work which the muscle can yield.

The amount of work is estimated by the weight which a muscle raises multiplied into the number of times it is lifted and the height it is raised each time. These are ascertained by

[1] Wedenskii, *Archiv f. Anat. u. Physiol.* Phys. Abthlg. 1883, p. 325.

registering the contractions on a slowly revolving drum, as in Fig. 46, which shows the rapid exhaustion of a muscle poisoned by carbolic acid as compared with a normal one. The rapid exhaustion of muscles may also be observed in the form of the tetanus curve which, under the influence of such poisons, falls much more rapidly in height than that of the normal muscle.

This group contains a number of drugs having an emetic action.[1] These are: apomorphine, asclepiadine, cyclamine, delphinine, sanguinarine, and saponine, copper, zinc, and cadmium. Antimony has a somewhat similar action, but only in large doses, and after a great length of time. Arsenic, platinum, and probably mercury, act in the same way as antimony.[2] Tin, nickel,[3] cobalt,[3] manganese,[2] aluminium, and magnesium, have little or no action on muscle. Large doses of iron are nearly as powerful as arsenic, but in small doses it rather increases the amount of work the muscle can do.

Carbonic oxide at the atmospheric pressure does not affect muscular contractility, but abolishes it at a pressure of five atmospheres.

Perhaps we may take as a subdivision of this group those poisons which lessen the contractile power of the muscle without

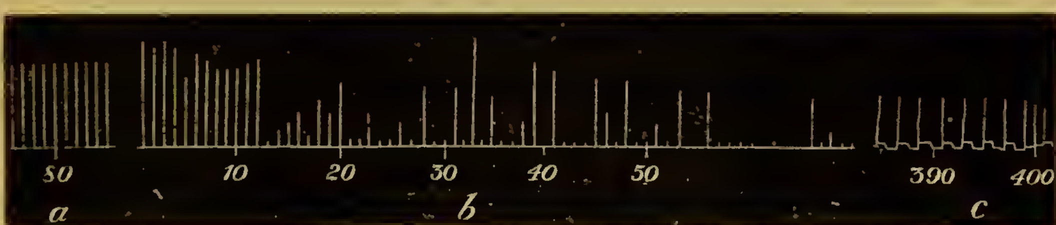

FIG. 47.—(After Harnack.) Shows the action of lead on muscle. *a* shows the contraction of a normal muscle after eighty stimulations; *b*, the irregular contractions of a muscle poisoned by lead after ten to fifty stimulations; *c* shows the slow relaxation of the muscle after contraction in a muscle poisoned by lead after numerous stimulations.

altering its irritability. When a muscle poisoned by one of these is stimulated, it may contract quite as readily as a normal muscle, provided the weight that it has to raise is but slight, but it cannot raise such a heavy weight as a normal muscle. This is tested by loading it with a given weight, and the slightest contraction is ascertained by adjusting the lever of the myograph in such a way that if raised in the very least it breaks a connection in an electrical current and causes a bell to ring. By this means contractions quite imperceptible to the eye are readily appreciated. Digitalis has an action of this sort, as I found in some experiments carried on under the direction of Professor J. Rosenthal in 1868, but not published.

Group II. contains salts of potassium, lithium, ammonium,

[1] Harnack, *Archiv f. exp. Path. u. Pharm.*, Bd. ii. p. 299, and iii. p. 44.
[2] Kobert, *Arch. f. exp. Path. u. Pharm.*, Bd. xv. p. 22, and xvi. p. 361.
[3] Anderson Stuart, *Journ. of Anat. and Physiol.*, vol. xvii. p. 89.

quinine, cinchonine, oil of mace, alcohol in large doses, chloroform, &c.

Chloral, chloroform, and ether also belong to this group, but they might also be reckoned as belonging to Group IV., for they slow the ascent, lessen the height, and prolong the descent of the curve. Curare has a similar action.

It is usually stated that curare, while it paralyses motor nerves, leaves the excitability of the muscles unaffected, but this appears not to be quite correct, for, when very weak currents are employed, the muscle loses its excitability by them before the nerve, and the contractions of the muscle at the same time become unequal. It is perhaps not yet perfectly certain how far these appearances are due to the curare, and how far to the gradual death of the muscle.[1]

Group III. contains poisons of which lead is a typical example. These poisons cause the muscular contractions to become very unequal, although the stimuli are equal and regular. Emetine and cocaine have a similar action to lead. This action is probably due only to the gradual death of the muscle. It is produced also by ptomaïnes, and it may occur in muscles which are simply dying without being poisoned at all.[2]

Group IV. contains poisons which alter the form of the curve to a marked extent.

The action of veratrine is very peculiar: it does not lessen the rapidity of contraction, and even increases the height of the curve, but it prolongs the descent to an enormous extent.

FIG. 48.—Tracing of the contraction curve of a muscle poisoned by veratrine, showing enormous prolongation of the contraction, the recording cylinder making many complete revolutions before the muscle is completely relaxed.

This action of veratrine is most marked at moderate temperatures.

It is much diminished, and sometimes entirely removed, by cold; and it disappears also when the temperature of the muscle is considerably raised. When the muscle which has been cooled or heated is again brought back to a moderate temperature, the contracture sometimes returns, but occasionally does not, the

[1] Marey, *Travaux du Laboratoire*, 1878, p. 157.
[2] Mosso, *Les Ptomaïnes*, Turin, 1883.

effect of veratrine on the muscle appearing to be sometimes, but by no means always, destroyed by the heat or cold to which the muscle has been exposed.[1]

The result of this exceedingly prolonged contraction is that a frog poisoned with veratrine is able to jump with considerable power, but the extensor muscles, by which the movement is executed, remain contracted instead of relaxing. The animal therefore lies extended and stiff, and is only able very slowly to draw its legs up towards the body. After they have been drawn up, the flexors in their turn remain contracted for a while, and so the animal is unable to jump until some time further has elapsed.

Another remarkable point about the action of veratrine on muscle is, that although a single contraction lasts so long as seriously to interfere with the power of co-ordinated movement, yet, if the muscle is made to contract a few times in rapid succession, the effect of the veratrine disappears, and it again acts normally. After a short rest the effect of veratrine again reappears.

A similar action to that of veratrine is exerted by salts of barium, which, when locally applied, cause the muscle to describe

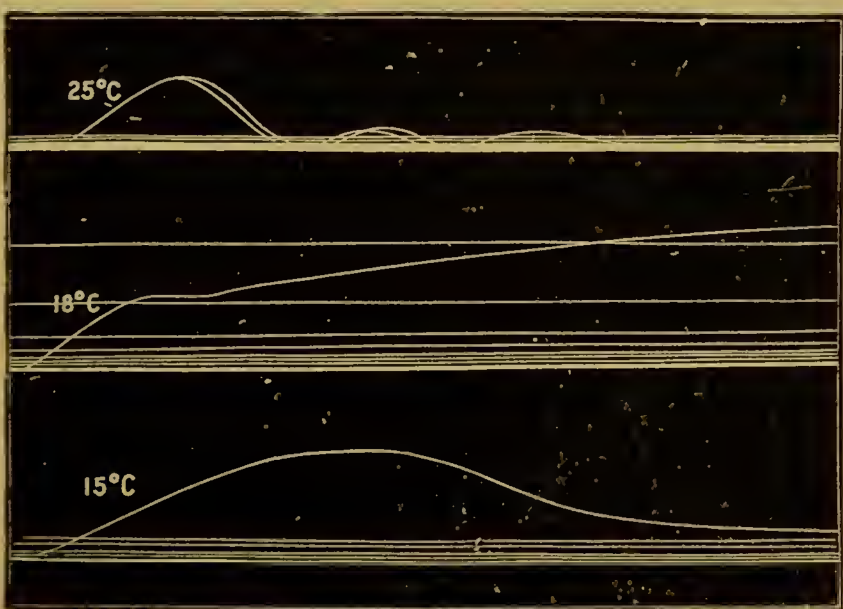

FIG. 49.—Tracing of the contraction curves of a muscle poisoned by veratrine, showing the peculiarly elongated curve at a moderate temperature, and its restoration nearly to the normal by cooling and heating.

a curve resembling that of veratrine, not only in its form, but in the alterations produced by temperature and in its temporary disappearance after repeated contractions. A similar action is exerted also, though to a less extent, by strontium and calcium. Salts of potassium may at first increase the height of contraction, but afterwards both moderate and large doses

[1] Brunton and Cash, *Journ. of Physiol.*, vol. iv. p. 1, and *Centralblatt f. d. med. Wiss.*, 1883, No. 6.

shorten the muscular curve, and lessen its height, so as finally to abolish its contractile power altogether. When applied to a muscle poisoned by veratrine, barium, strontium, or calcium, salts of potassium remove the excessive prolongation of the contraction which these drugs occasion, and restore the muscular curve again to its normal.[1]

Although veratrine alters the form of the muscular curve so greatly, it does not (excepting in large doses) paralyse the muscle, so that when a poisoned muscle is made to contract at regular intervals for a length of time, it is able to do as much work as a normal one.

Nearly allied to this is another group of muscular poisons, some of which have already been mentioned as a sub-division of Group I. It contains: digitalin, digitalein, digitaleresin, digitoxin, toxiresin, scillain, helleborein, oleandrin, adonidin, neriodorin, and neriodorein. Tanghinia, thevetin, and frynin, or toad poison, probably also belong to this class.

These drugs do not lessen the irritability of muscle, but appear to alter somewhat the form of the muscle curve, somewhat in the same way, but to a less extent than substances of the veratrine group. Some of them when applied in a concentrated form directly to the muscle cause a condition of rigor. This is especially the case with caffeine and digitalin. This rigor is well marked in the *rana temporaria*, and only to a comparatively slight extent in the *rana esculenta*. Although caffeine in concentrated solution produces *rigor mortis* in the muscle, yet in very dilute solutions it is a muscular stimulant, and as such is included in the sixth group.

Group V. contains physostigmine, which increases the excitability of muscle to slight stimuli, but does not increase the amount of work it can do; on the contrary, in large doses it diminishes it.

Group VI.—Poisons belonging to this group in small doses increase muscular work, and cause the muscle to recover rapidly after exhaustion. Creatin has this power to a great extent; hypoxanthin has it also, though less powerfully. The effect of these substances is very interesting, because they are products of muscular waste. They also occur in beef-tea, and their action appears to show that beef-tea assists muscular power, as well as acts as a nervous stimulant.

Other members of this group are caffeine and glycogen: these have great power to increase muscular work. The relation of caffeine to hypoxanthin is very interesting. Xanthin, which is another substance derived from muscles, differs from hypoxanthin in containing one atom more oxygen. Theobromine, the active principle of cocoa, is dimethylxanthine; and caffeine, the

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[1] Brunton and Cash, *Proc. Roy. Soc.*, 1883.

active principle of tea and coffee, is trimethylxanthine. The restorative effects of beef-tea, coffee, tea, and cocoa have long been recognised empirically, although their action could not be explained. It now seems not at all improbable that it may be partly due to their restorative effect on the muscle.

Massage.—The effect of kneading a muscle so as to remove the waste products from it is very extraordinary.

When the muscles of an uninjured frog are stimulated to contraction by the rhythmic application of maximal induction currents until they are exhausted and no longer contract, kneading them, or massage, restores their contractility so that their contractions are nearly as powerful as at first, while simple rest without massage has very little restorative effect. In man also, while a rest of fifteen minutes after exhausting labour had very little restorative action, massage during the same period increased double the work that could be done. Massage has a similar action to very complete and perfect circulation through the muscle, in removing the waste products and restoring its power.[1]

Propagation of the Contraction Wave in Muscle.—When a muscle is irritated at one point, the contraction wave which occurs at that point is conducted along the muscle in both directions.

This contraction wave, like that which occurs in the contractile tissue of the medusa, is independent of the nervous system. The completeness with which it is conducted, and the quickness with which it subsides at each point, are closely connected with the rapidity of the conduction, and they are also injuriously affected by anything which impairs it. It diminishes during the death of the muscle, and it is lessened also by fatigue, by cold, and by injury, such as excessive stimulation. Certain poisons also lessen it, as cyanide of potassium, veratrine, and upas antiar.[2]

Heat increases the rapidity of the conduction.

Rhythmical Contraction of Muscle.—Rhythmical contraction is frequently regarded as a function of involuntary muscular fibre only; this, however, is not the case, for it is observed also in voluntary muscles. Rhythmical contraction of involuntary muscle is seen in the trachea,[3] and is well marked in the heart and blood-vessels. It is very distinct in the intestines and bladder, and becomes still more marked after the influence of the central nervous system has been destroyed. In the case of the sphincter ani, for example, the rhythm is strong and regular, especially after the nerves have

[1] Zabludowski, *Central. f. d. med. Wiss.*, 1883, No. 14, p. 241.

[2] Aeby, *Untersuchungen über die Fortpflanzungsgeschwindigkeit der Reizungen der quergestreiften Muskelfaser.* Braunschweig, 1862, p. 52.

[3] Horwath, *Pflüger's Archiv*, 1875, vol. xiii. p. 508.

been divided and the muscle subjected to some mechanical distension by the introduction of the finger.

In voluntary muscle the tendency to large rhythmical pulsations is slight, although we see rapid contractions occurring in tetanus.

The number of impulses sent down to the muscles along the motor nerves, from the spinal cord, is about 10 per second in the dog. If more numerous impulses are sent down from the cerebral cortex, or corona radiata, or if more numerous stimuli are applied to the spinal cord itself, summation appears to occur in the cells of the spinal cord, and only 10 impulses per second are sent out.[1]

From the observations of Wedenskii, that irritation of the motor nerve of a muscle by exceedingly rapid stimuli still produces the same number of contractions in the muscle, it seems probable that this rate of contraction is due to the constitution

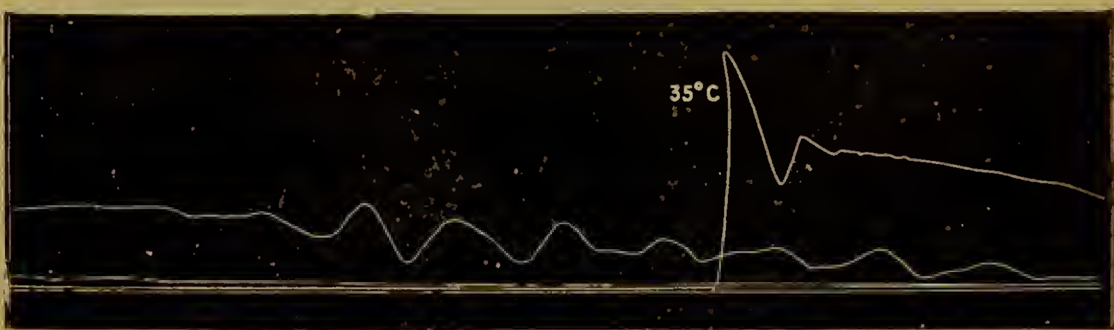

FIG. 50.—Tracing of the contraction curve of a muscle poisoned by veratrine and exposed to a high temperature. The poison tends to cause prolonged contraction, and the high temperature to cause rapid relaxation of the muscle. The result is a somewhat rhythmical spontaneous contraction. The muscle was only irritated at the very beginning of the first contraction.

either of the muscle itself, or of the nerve-endings within it. Under certain circumstances, however, the voluntary muscle may be made to contract with a slow rhythmical movement of considerable extent, and closely resembling that of involuntary muscular fibre.

Thus voluntary muscle treated by veratrine tends to remain contracted for a length of time like an involuntary muscle: heat has a tendency to cause its relaxation, and sometimes, as is seen in the accompanying figure (Fig. 50), these contending influences produce in the voluntary muscle a tendency to marked rhythmical contraction.

A still more remarkable phenomenon has been noticed by Kühne,[2] who finds that when the uninjured sartorius of a frog is placed in a solution of 5 grammes NaCl, and 2·5 grammes of common alkaline crystallised phosphate of sodium in a litre of

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[1] Horsley and Schäfer, *Proc. Roy. Soc.*, vol. xxxix. p. 406.

[2] *Untersuchungen aus dem Physiologischen Institute der Universität Heidelberg.* Sonderabdruck, 1879, p. 16.

water, it begins to contract at once, and after it has been transversely divided it beats with the regularity of the heart.

The effect of various substances on the rhythmic action of muscle treated in this way has been investigated by Biedermann. He finds that the best fluid for the sartorius is 5 grammes NaCl, 2–2·5 grammes of Na_2HPO_4, ·04–·05 gramme of Na_2CO_3. A low temperature, not rising above 10° C., is best. The lower the temperature the slower is the rhythm and the more extensive the contraction. Heat quickens the rhythm and lessens the contraction. At about 18° to 20° C. the contractions become rapid and indistinct. When caustic soda is used instead of carbonate, the effect is similar, but the muscle dies much more quickly. Potassium carbonate and other potassium salts only cause pulsations when greatly diluted. Lactic acid stops the pulsations; alkaline NaCl solution again restores them. Veratrine and digitalin in a solution of NaCl also cause pulsations.[1]

Schönlein finds that, with a certain strength of current interrupted about 880 times in a second, the muscles of the water beetle are not tetanised, but contract rhythmically from two to six times in a second.[2]

Biedermann has succeeded in making a voluntary muscle, such as the sartorius, contract rhythmically by applying a solution of sodium bicarbonate (2 per cent.) to the tibial end, and then passing a constant ascending current through the muscle.[3]

Pathology of Tremor.

Rapid alternation of contraction and relaxation, or tremor, may be observed to affect either—(*a*) a few bundles of muscular fibres, (*b*) a single muscle, or (*c*) groups of muscles.

The tremors affecting a few bundles of fibres, or fibrillary twitchings, may occur in excised muscles, and are probably due to some conditions of the muscular fibre allied to those which have already been considered (p. 132). They may occur also in muscles which still remain in the living animal after the nerve has been cut, more especially in the muscles of the tongue after section of the hypoglossal nerve, or in the muscles of the face after section of the facial nerve.[4]

Tremors affecting groups of muscles occur, in some cases, when the limbs are at rest, and cease during voluntary movement, as in paralysis agitans; or may cease entirely when the limb is at rest, and only come on when the muscles are put in

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[1] *Sitzungsber. d. Wiener Akad.*, Abth. lxxxii. p. 257-275.
[2] Schönlein, du Bois Reymond's *Archiv*, 1882, p. 357.
[3] *Sitzungsber. d. Wien. Akad.*, Bd. lxxxvii., Abt. iii., March 1883.
[4] They may possibly be regarded as due to disturbance of the normal relations between longitudinal and transverse contraction in muscular substance.

action, as in disseminated sclerosis and in mercurial tremor. As already mentioned, a certain number of motor impulses per second are required to keep a muscle steadily contracted.

It is evident that, if the stimuli proceeding to the muscles from the nerve-centre should be too few, tremor, and not steady contraction, of the muscle will occur. And the same will be the case if any change in the muscle itself should render the duration of each single contraction less than usual.

But in all co-ordinated movements a number of muscles, the actions of which are antagonistic to each other, are brought into play; and it is by the proper adjustment of these antagonistic actions that the performance of delicate movements becomes possible. Unless the amount of contraction of each of these muscles is exactly graduated, there will be a tendency to oscillatory movement. As the amount of contraction in each muscle, or group of muscles, is regulated by the stimuli sent down to it from the nerve-centres, it is evident that if the motor cells supplying one group of muscles be affected more than those which supply the antagonistic or regulating muscles, inco-ordination, and possibly tremor, will occur. The pathology of tremor is still, however, very obscure.

Treatment of Tremor.—If tremor should depend upon insufficient rapidity of the stimuli passing to the muscles from the nerve-centres, it is evident that any drug which, like veratrine, will increase the duration of each individual contraction, is likely to be of use. Acting upon this idea, Dr. Ferris has used veratrine in cases of tremor due to alcoholism, disseminated sclerosis, and weakness after typhoid fever. Although this treatment was successful in all these diseases, it does not seem quite certain that the utility of the medicine may not be partially due to its action on the spinal cord as well as on the muscles themselves. In one case of tremor, occurring at the commencement of general paralysis, I have given salts of calcium with the same object with the apparent result of arresting the tremor. I had intended to use barium, but the tremor ceasing for many months with calcium, I have not proceeded to use anything else.

Connection between Chemical Constitution and Physiological Action on Muscle.

I have already mentioned (p. 29) that one can hardly look for a general relation between the atomic weights of metals and their lethal activity, so that what we want is really a knowledge of the particular relationship of each group of elements to the organs and tissues of the body.

In such an investigation it seems natural to take the muscles first, then the motor nerves, afterwards the nerve-centres and individual organs. A number of experiments have been made by

Cash and myself in order to do this for the alkalis and alkaline earths, and we have found that the contractile power of muscle, as shown by the height of the curve, is increased by rubidium, ammonium, potassium, and cæsium. It is slightly increased or unaffected by sodium, excepting in large doses, and is almost invariably diminished by lithium.

The duration of contraction, as shown by the length of the curve, is increased by rubidium in large doses, ammonium, sodium, and cæsium. It is shortened by ammonium, lithium, rubidium in small doses, and by potassium.

The contracture, or viscosity, is increased by rubidium in large doses, ammonium, lithium, and sodium. It is diminished by rubidium in small doses, ammonium, cæsium, and potassium.

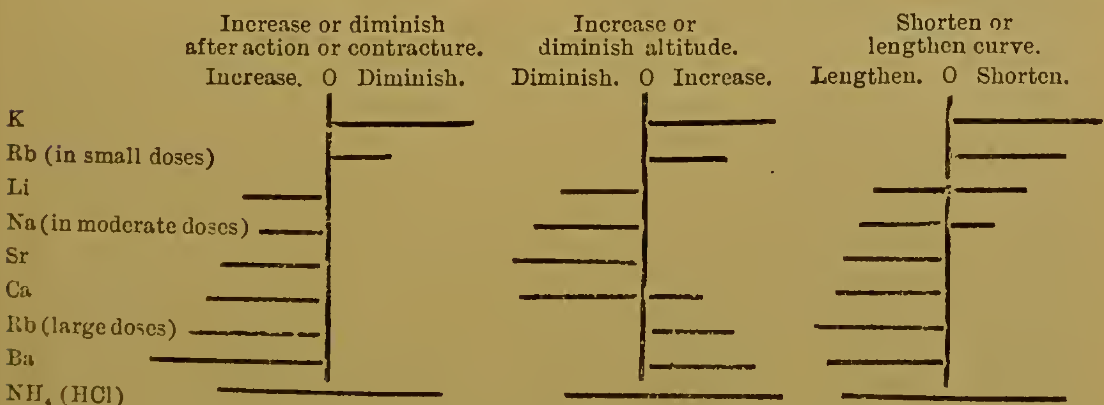
Both ammonium and rubidium have two actions on muscle of an opposite character, sometimes increasing and sometimes diminishing both the duration of the contraction and of the contracture, or viscosity, which remains after the ordinary contraction has ceased. In the case of rubidium this appears to depend upon the dose, but we were not satisfied that it was so entirely in the case of ammonium salts.

In regard to the action of the alkaline-earths and earths, we found that the contractile power of muscle is increased by barium, erbium, and lanthanum. It is sometimes increased and sometimes diminished by yttrium and calcium. It is diminished by didymium, strontium, and beryllium.

The duration of contraction is increased by barium, calcium, strontium, yttrium, and erbium. It is unaffected, or slightly diminished, by beryllium, didymium, and lanthanum.

Contracture is increased by barium, calcium, strontium, yttrium, and beryllium.

The contracture produced by barium is enormous, resembling that produced by veratrine. It is, like that of veratrine, diminished by heat, cold, and potash, and may be abolished by these



agents. It is by no means so well marked when the drug is injected into the circulation as when locally applied to the muscle.

The action of some of the more important of those drugs can

be graphically represented by a spiral, the terminal members of which are potassium and barium, and these two are, to a certain extent, connected by ammonium as an intermediate link.

The effect of one member of one of these groups may be diminished or increased by the subsequent application of another. Potassium shortens the elongated curves caused by barium, calcium, sodium in large doses, and lithium, and reduces the contracture which these substances cause. The veratrine-like curve of barium is counteracted by almost all the substances which produce a shorter curve than itself.

Action of Drugs on Muscle is Relative and not Absolute.

In considering the action of drugs on muscle, the first point which comes clearly out is that the action of a drug on the muscle is not absolute, but merely relative. Thus veratrine and salts of barium are not to be regarded as absolute muscle-poisons—they are only poisons under certain conditions of quantity and of temperature. An exceedingly small dose of veratrine, instead of acting as a poison to muscle, acts rather as a food, and restores it when exhausted. Caffeine likewise in small doses has a restorative action, while in large doses it is a powerful poison. Veratrine and barium in moderate doses and at moderate temperatures are powerful muscular poisons, but at low temperatures and at high temperatures their action is to a great extent, or even completely, abolished. Nay more, moderate quantities of barium salts at moderate temperatures are poisonous to the normal muscle, but they are restorative to the muscle whose composition and functions have been already altered by rubidium. Acids and alkalis also produce an effect on muscle, but their effect depends upon whether they are applied to the normal muscle or to one previously treated with a substance having an opposite reaction.

It is evident, then, that the whole question of the action of drugs on muscle is one involving the relation of the drug to the muscle at the time of application, and we must expect that if the temperature is different from the normal, or if the composition of the muscle should vary, the action of the drug will vary likewise. Now the composition of all the muscles in the body is not the same, as has been shown by Toldt and Nowak,[1] and the composition of the ash obtained by the combustion of different animals is also different, as has been shown by Lawes and Gilbert.[2] We may therefore expect that muscular poisons will not act alike at the normal temperature and in febrile conditions, nor alike upon all the muscles of an animal; nor will they

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[1] Quoted by Seegen, *Wien. Akad. Ber.* lxiii. Abt. ii., 11-43.

[2] *Proc. Roy. Soc.*, xxxv., p. 344.

always have the same action upon different animals—the relations being different, the effects will be different. The effect of poisons upon muscles will also vary according to the chemical composition of the tissue at the time. This composition may probably, to a certain extent, be altered by feeding—at least as far as regards the proportions of inorganic ingredients. We know that the quantity of sodium chloride in the body can be increased, for if an animal be fed with a larger quantity of salt than usual, it does not at once begin to excrete, but stores it up for two or three days, and then the excretion increases. After the administration of the salt has been stopped the excretion continues large for two or three days, and then returns again to the lower standard. It seemed probable that similar retention would take place with potash, and if this were so, we might expect to counteract to a great extent the effect of barium by feeding an animal on potash for some time before administering the barium. On trying this, Cash and I have found that this is the case to a certain extent, and although we have not been able completely to counteract the effect of a large dose of barium so as to prevent death from a lethal dose, we have been able to modify and diminish its action by the administration of potash for several days previously, so that the characteristic symptoms of barium poisoning do not occur until some hours after they would otherwise do so, and thus life is prolonged though not preserved.

Action of Drugs on Involuntary Muscular Fibre.

Contraction.—Involuntary muscles, with the exception of the heart, differ from voluntary not only in their anatomical structure but in their functional activity: instead of contracting or relaxing rapidly, both their contraction and relaxation are slow. We have seen that although voluntary muscle occasionally exhibits spontaneous rhythmical contractions, yet these occur only under exceptional circumstances, and but rarely. Involuntary muscle, on the other hand, has a much greater tendency to rhythmical contraction, although it may be regarded as doubtful whether some stimulus, however slight, is not required to induce this rhythm even in involuntary muscle. It has been already mentioned that the contractile tissue of medusa will beat rhythmically so long as it is connected with motor ganglia. When these ganglia are removed, the contractions cease, but will again reappear, notwithstanding the absence of the ganglia, if a constant stimulus be applied to the contractile tissue itself. This shows that the conditions for rhythm are contained in contractile tissue itself—that the rhythm may be independent of the ganglia with which the contractile tissue is connected (p. 113). The same appears to be the case with involuntary muscular fibre generally.

The ventricle of the frog's heart, containing ganglia, will beat rhythmically for a length of time after its removal from the body. If the ganglia which lie close to the auriculo-ventricular groove be cut off, the rhythmical action will cease just as in the medusa when the marginal ganglia are removed; but if a constant stimulus be applied to the apex of the heart, as for example by passing a constant current through it, or by distending it with serum, its rhythmical movement will again commence, mechanical distension appearing to have upon it the same exciting action that a little acid added to the water has upon the nerveless bell of the medusa.

The excitability of involuntary muscular fibre appears to be increased by small doses of atropine; for when the ganglia of the frog's heart are removed the apex, instead of stopping immediately, will give a few beats before it stops if atropine has been previously given, and mechanical stimuli cause more beats in the atropinised than in the normal apex.[1]

Effect of Stimuli.—Mechanical distension appears to be one of the most powerful of all stimuli to excite rhythmical contraction in involuntary muscular fibre.

Luchsinger observed distinct pulsation in the veins of a bat's wing twenty hours after the death of the animal, if artificial circulation was kept up. This appears to show that the power of rhythmical contraction resides in the muscular fibres of the veins, as it does in the nerveless apex of the frog's heart, and the contractile tissue of the medusa; but here also an external stimulus appears to be required to induce contraction. When the pressure by which artificial circulation was maintained fell to zero, the pulsation stopped, but if it were raised to forty or fifty centimetres of water, so as to distend the vascular wall, rhythmical pulsation again commenced. It appears possible, however, that when involuntary muscular fibre is perfectly healthy and possesses the highest degree of irritability, it may contract rhythmically without any extra stimulus. Thus Engelmann[2] observed that the ureter, in which he could find no nerves at all, contracted rhythmically when freshly exposed, although it was not distended or subjected to any mechanical irritation; but if artificial respiration has been long kept up, and the animal is exhausted, so that the excitability of the ureter is diminished, then the effect of minimum distension in increasing its rhythm becomes very evident.

Cold causes the isolated non-striated muscles of animals to relax. **Heat** causes them to contract.[3]

The influence of heat and cold, however, does not seem to be constant, and in the non-striated muscle of frogs they have an

[1] Langendorff, *Archiv f. Anat. u. Phys.* Physiolog., Abtg. 1886, p. 267.
[2] *Pflüger's Archiv*, 1869, Bd. 11, p. 251.
[3] Luchsinger and Sokoloff, *Pflüger's Archiv*, Bd. 26, p. 465.

opposite connection to that just described. It is probable that the different results may depend to a great extent upon the amount of heat or cold applied, and its relation to the condition of the tissues at the time of application; for mechanical stimulation has also an opposite effect, according to its amount; and while gentle stimulation of involuntary muscular fibre, such as that of the small blood-vessels, causes dilatation, more powerful irritation produces contraction.[1]

The influence of various drugs upon involuntary muscular fibre, as seen in the contraction of the blood-vessels, will be described when considering the circulation.

The Relation of the Contractile Tissue to the Nerves is different in voluntary and involuntary muscular fibre. In the latter there are no end plates, but the terminal twigs form a plexus around the fibres. The motor nerves of involuntary muscular fibre appear to be affected by atropine and its congeners in a similar way to those of voluntary muscle by curare. There appears also to be a certain relationship between the atropine and curare group. Small doses of atropine paralyse the motor nerves of involuntary muscle, while very large doses of curare are required. The converse is the case with voluntary muscle. These effects are usually supposed to be due to a definite paralysing action on the nerves themselves. There are difficulties, however, in the way of this hypothesis, and a more probable one, perhaps, is that these drugs disturb the relations between the nerves and the muscular fibres which they excite. On the idea of a specific action it seems hard to explain the results obtained by Szpilman and Luchsinger,[2] who found that atropine produces paralysis of the motor fibres of the vagi supplying the œsophagus, only in those parts of it where involuntary muscular fibre is present. Thus the œsophagus of the frog and the crop of birds consist of involuntary muscular fibre, and atropine destroys the motor power of the vagus over them. The œsophagus of the dog and rabbit contains striated muscular fibre, and atropine does not paralyse the motor nerves. The œsophagus of the cat contains striated muscular fibres in its upper three-fourths, and non-striated in its lower fourth; atropine destroys the motor action of the vagus upon the lower fourth, but not upon the upper part.[3]

Propagation of Contraction Waves.—Although involuntary muscular fibre consists of short cells and not of long fibres like voluntary muscle, yet the contraction wave may be propagated along a strip of involuntary muscular tissue in both directions from the point of irritation, just as in voluntary muscle or in the contractile tissue of medusæ. This wave is transmitted

[1] Sigmund Meyer, *Hermann's Handb. d. Physiol.*, Bd. 5, Theil ii., p. 476.
[2] Szpilman and Luchsinger, *Pflüger's Archiv*, Bd. 26, p. 459.
[3] *Ibid.* p. 249.

more slowly in involuntary than in voluntary muscle; and its rate in the involuntary muscle of the heart, though slower than in ordinary striated muscle, is quicker than in unstriated muscle, so that in this respect the heart is intermediary between the two.[1]

The passage of contraction waves in involuntary muscular fibre is affected by the same conditions as voluntary muscle, the conduction of the contractile wave being rendered slower by fatigue and cold, while it is quickened by heat.

Cold and fatigue also render the rhythmical pulsations smaller and longer, while heat has an opposite effect. The passage of the contraction wave may also be diminished or arrested by section or pressure, just as in the contractile tissue of medusæ,[2] so that instead of each contraction wave passing the block produced by the sections or compression, only one out of several, or none at all, may pass. The proportion passing the block depends upon its completeness. If the tissue forming the bridge be dry as well as narrow, the block becomes more complete, and may be again diminished by moistening. Variations in the strength of the stimulus do not affect the passage of the contraction wave over the block, so that it would appear that the injury caused by the section, along with the narrowing of the conduction path, retards the re-establishment of the conductive power.

In experiments made upon the heart of a tortoise cut into a strip, it has been found by Gaskell that stimulation of the **vagus** removes the block, quickens the recovery of the tissue, and causes every contraction wave to pass. The effect upon the muscle therefore seems to be trophic.

A **weak interrupted current** applied to the muscle directly has the same action as stimulation of the vagus, i.e. it increases the conducting power of the muscle. Sometimes, however, both the vagus and a weak interrupted current have an opposite effect, and diminish instead of increasing the conducting power.

An **artificial rhythm** may be induced in a strip of involuntary muscular fibre cut from the heart of the tortoise by passing a weak interrupted current through it and then stimulating it at one end by induction shocks, at intervals of about five seconds. After a while, if the induction shocks are discontinued, the muscle still continues to contract rhythmically at the same rate. These contractions, at first weak, afterwards become strong, and may last for many hours. Both the conducting and the contractile power of the muscle are diminished by muscarine. When a strip of it is stimulated by induction-shocks applied to one end, the contraction wave passes quickly along; but muscarine appears to

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[1] *Hermann's Handbuch d. Physiologie*, Bd. 1, p. 56.

[2] Engelmann, *Pflüger's Archiv*, 1875, Bd. 11, p. 465; Gaskell, *Journal of Physiology*, vol. iii. p. 367.

block its transmission, so that while the part of the muscle between the electrodes contracts at every shock, the rest of the muscle contracts only at every second one. A weak interrupted current then sent through the muscle may lower its conducting power and still further reduce the force of the contractions, and not only block the passage of most of the contraction waves from the point of excitation, but may even prevent the contraction of the excited part itself.

Atropine has an opposite action and appears to increase the conducting power of involuntary muscle, so that when applied to a strip of the heart, the conducting power of which has been diminished by muscarine, the contractility is at once increased, and each contraction wave passes over the whole muscular strip each time that a single point is irritated. Large doses, however, appear to have a depressant action on the muscle.

Hypothetical Considerations regarding the Action of Drugs on Muscle.

The modifications which drugs produce in the functions of the animal body and of its parts are so numerous and varied that we are unable fully to explain them on the basis of our present physiological knowledge. The results of pharmacological experiments furnish us indeed with a number of additional facts regarding the functions of organs and tissues which will ultimately lead us to a more correct and thorough knowledge of their physiology. At present, however, we can only explain them hypothetically, and, indeed, in many cases we can do little more than guess at the explanation.

The advantage to be gained from hypothetical explanations is that hypotheses not only lead to further experiment, but serve as guides for experiments, by which, if false, they may be soon disproved, or, if true, may be maintained.

The disadvantage of hypotheses is that they are sometimes apt to be taken for facts, and being made use of as bases for further speculation, may lead more and more astray from the truth. While bearing in mind the danger of speculation, it may be useful to make some guesses at the mode of action of drugs upon the muscle as guides to further research.

The most striking point about muscle is the motor function which it exercises by contracting, and the nature of its contraction must engage our attention. Throughout the universe we find that motion of nearly all sorts resolves itself into a series of vibrations, and the question arises whether the motion of muscle cannot be explained in the same way.

When a muscle is stimulated it contracts and relaxes once, describing a wave-like curve upon the revolving cylinder. Frequently this first wave is followed by a second, and sometimes even by a third, which are usually ascribed to the simple elasticity of the muscle. Sometimes we can notice that the single contraction wave appears really to consist of two or more partially superimposed on each other, and sometimes we may find two distinct waves arise from one stimulation.

When a muscle is in a state of tetanic contraction it appears to the eye to be perfectly quiet, yet we know that during this period of apparent rest the muscle is in a state of vibration, alternately tending to contract and elongate. These vibrations may succeed one another with a rapidity such that the muscle appears to the eye to be motionless, while a tracing taken upon the revolving cylinder shows distinct successive waves. If the vibrations are still more rapid, the waves may disappear, and we get the muscle describing a straight line. But even when a muscle is entirely relaxed, its parts may

be in a state of vibration quite as continuous as in tetanic contraction. This is seen by examining muscular fibre under the microscope. The phenomenon which then presents itself was described by Porret and is often known by his name. On passing a constant current through a thin muscular slip a contraction is seen when the current is closed. During the whole time of the passage of the current, the muscle, to the naked eye, appears to be perfectly at rest, but under the microscope its parts are seen to be in constant motion, presenting an appearance almost exactly similar to the waving of a field of corn on a windy day, or to the motion of rows of cilia. At the same time an actual transference of material takes place in the muscle: the end next the positive pole growing smaller, and the end next the negative pole growing larger. When the current is suddenly reversed, a sudden contraction of the whole muscle takes place, and it then returns to apparent rest; but microscopic observatión shows the same cilia-like motion as before, but in an opposite direction.

This phenomenon reminds one very strongly of the crowding together of carriages in a railway train when it is set in motion or stopped by the locomotive pushing behind or stopping in front. We know that the apparent steady movement of the train is due to the backward and forward vibration of the piston in the cylinders of the locomotive, and the question occurs whether the contraction of the muscle as a whole at the moment of opening and breaking the current, is not due to an interference with the rhythmical vibration of its parts. The question also arises whether these vibrations are not to a great extent dependent upon the molecular weight of its constituents. This seems to a certain extent to be indicated by the curious relations between the effects of the alkalis, alkaline earths, and certain metals upon muscle. Thus Cash and I have found that potassium and calcium neutralise the action of each other upon muscle, and if the hypothesis just expressed be correct we should expect that metals having a similar molecular weight to a mixture of calcium and potassium would have no action upon muscle. This appears to be the case. In researches made in Professor Schmiedeberg's laboratory, Anderson Stewart found that nickel and cobalt had no action upon muscle, and White found that tin also had little or none. On comparing then the atomic weights of potassium (39), calcium (40), nickel (59), cobalt (59), and tin (118), we get the following relationships:

$$K_2\ (78) + Ca\ (40) = Ni_2\ (118), \text{ or, } Co_2\ (118), \text{ or, } Sn\ (118.)$$

Sodium in large doses lengthens the curve and increases the contracture when applied to a normal muscle. It adds to the length of the long curves caused by calcium and strontium. Rubidium in large doses produces a long curve with enormous contracture almost like that of barium. One would naturally have expected that the rubidium and barium would have increased each other's effect like sodium, calcium, or strontium; but the reverse is the case, for the abnormal curve caused by rubidium is reduced to the normal by the application of barium. If barium be applied to a greater extent than is sufficient to antagonise rubidium, it first abolishes the prolonged rubidium curve, reducing it to the normal, and then again elongates it, producing its own characteristic curve. Calcium and strontium, which also prolong the curve, though to a less extent than barium, do not antagonise one another's effect—they rather increase it; but calcium reduces the barium curve to the normal before causing its own peculiar curve. At first sight these results seem to be independent of any rule, but a curious relation is to be observed between the atomic weights of these substances. Thus we have seen that rubidium in large doses has the same effect as barium in causing a veratrine-like curve, but barium destroys the effect of rubidium before producing its own effect. On comparing the atomic weights of these elements we find that eight atoms of rubidium have nearly the same weight as five of barium, and by subtracting one from the other we get almost no remainder. Thus,

$$\begin{aligned} Ba\ 137 \times 5 &= 685 \\ Rb\ 85{\cdot}4 \times 8 &= 683{\cdot}2 \end{aligned}$$

Potassium is, as we know, an important constituent of muscle, and it seems possible that the reduction in the barium-curve which calcium causes may be due to their union having resulted in a substance whose molecular weight is a multiple of that of potassium. Thus,

$$\begin{array}{ll} \text{Ba } 137 \times 2 = 274 - \text{Ca } 40 = & 234 \\ \text{K } \quad 39 \times 6 = & 234 \end{array}$$

The alterations which occur in voluntary muscle from the action of such substances as calcium or barium appear to approximate it to some extent to involuntary muscle. Voluntary muscle is chiefly characterised by sudden and rapid contraction and relaxation. Involuntary muscle usually contracts and relaxes slowly. In the slowness of its relaxation, at least, the muscle poisoned by barium or calcium approaches involuntary muscle.

The power of summation which contractile tissues possess is strongly suggestive of the idea that rhythmical vibrations of gradually increasing intensity are going on within the tissue even before any movement becomes visible. A pendulum very gently struck at proper intervals will gradually begin to oscillate through a larger and larger arc. If touched on one side while oscillating, the effect of the touch will depend upon the time at which the touch is applied, for at one period of oscillation it will tend to impede, and at another to assist the oscillation. Possibly some unseen rhythm in the muscle itself may be the cause of the curious variations in excitability observed in dying muscles and in muscles poisoned by lead. Two pendulums connected together will swing harmoniously if their rate of oscillation is the same, but if one be loaded so as to alter its rate of oscillation they will interfere with each other. Possibly the effect of poisons in paralysing nerves may be due rather to alteration in the relative rhythms of the nerve and muscle than to any specific destructive power on the terminations of the nerve itself.

The opposite effects which Gaskell has noticed the vagus nerve and a weak induced current to produce upon the conducting power of the cardiac muscle, sometimes increasing and sometimes diminishing it, may be due to the interference or coincidence of rhythm such as are discussed more fully farther on under the head of Inhibition.

It is impossible to say at present what the true cause of the curious rhythmical contractions of voluntary muscle is, but if we suppose that there is a transverse as well as a longitudinal contraction in muscle, we might regard the rhythmical contractions as resulting from the action of these two opposing forces.

It must be borne in mind that the considerations contained in this section are purely hypothetical, and their only use is to indicate the direction in which we may possibly look for an explanation of the action of medicines on muscle.

CHAPTER VI.

ACTION OF DRUGS ON NERVES.

General Action of Drugs on the Nervous System.

In low organisms the contractile protoplasm fulfils the functions of both nerve and muscle, but as we ascend in the scale differentiation becomes more and more complete. From their original common origin, however, we might expect that the poisons which act on the muscles would also act on the motor nerves, and *vice versâ*, and we should hardly expect any poison to act entirely on the one without affecting the other. This is to a considerable extent the case, for very many substances paralyse them both. But, as one would also expect from the differentiation they have undergone, muscle and nerve are not equally affected in the higher animals. Thus we find that although most of the salts of ammonium, and the iodides, chlorides, and sulphates of the compound ammonias into which methyl and ethyl enter, paralyse both muscle and nerve, yet they paralyse the nerve before the muscle. In some cases the nerve is affected so much before the muscle that at first sight it might appear that the nerve alone was paralysed and the muscle left unaffected. More careful observation, however, shows us that most of the compound ammonias, and probably most of the organic alkaloids, affect muscle, motor nerves, and nerve-centres, and, if their action can be continued long enough, will paralyse all three. The symptoms they produce may, however, be entirely different, because these depend upon the order in which the different parts of the nervous system are affected, as has already been pointed out at p. 26. The symptoms produced, for example, by strychnine and methyl-strychnine are utterly different, the former causing tetanic convulsions, and the latter gradually-increasing torpor, weakness, and paralysis. Strychnine stimulates the spinal cord, and methyl-strychnine paralyses the motor nerves; yet if their action continue long enough it is found that both of them will ultimately cause paralysis of both spinal cord and motor nerves. The final result is thus the same in both cases, but the order in which the various parts of the nervous system are affected is different.

In the example just given, the drugs appear to exert a selective influence on the spinal cord and motor nerves respectively, and consequently produce very different symptoms. But we find that a number of drugs appear to act upon muscles, motor nerves, and nerve-centres, in a given order, although there may be slight variations in the action of the individual drugs. These substances are generally found to act as protoplasmic poisons, arresting the movements of amœbæ and white blood-corpuscles, as well as proving fatal to higher animals.

In the protoplasm of these minute organisms we are unable at present to distinguish any evidences of differentiation. As we ascend in the animal kingdom we find a differentiation between

FIG. 51.—Diagram to illustrate Hughlings Jackson's views of the nervous system.

muscle, nerve, and nerve-centre; and the higher up we ascend in the scale the more complex do the nerve-centres become. As Hughlings Jackson has well put it, 'evolution is a passage from the most simple to the most complex, from the lowest to the highest centres.' It is a passage from the most automatic to the most voluntary; but the lowest centres are at the same time the most stable, or, as Jackson calls it, the 'most organised centres'; while the highest centres are the most unstable or least organised. This is represented diagrammatically in Fig. 51, where the centres for the heart and respiratory apparatus and for the

sphincters are represented as very simple in their organisation, but very stable, as indicated by the size of the ganglia and thickness of the nerves in the diagram. The spinal cord is represented as more complex, but with thinner lines, in order to show its lesser stability; while the high complexity and small stability of the cerebral cortex is indicated by the great number and thinness of the lines in the figure. According to Jackson, the lowest nervous centre extends from the aqueduct of Sylvius to the lower end of the spinal cord; and in this all parts of the body are directly represented, so that a discharge of nervous energy from any part of it only requires to overcome the resistance in the motor nerves and the muscles themselves. What he regards as the middle motor centres are evolved out of the lowest, and re-represent all parts of the body in more complex and special combinations. The highest centres evolved out of the middle re-re-represent all parts of the body in still more complex and special combinations. A discharge from the highest centres, in order to act on the periphery, has to overcome the resistance of the middle and lowest centres, as well as of the muscles.

In the action of such poisons as alcohol, the nervous system appears to be paralysed in inverse order of its development: the highest centres going first, next the middle, and then the lowest. After this comes paralysis of the motor nerves, and lastly of the muscles themselves. In the case of alcohol, the dose required to paralyse motor nerves and muscles is so great that, as a rule, we can only observe its effect by directly applying the drug to the nerves and muscles themselves. To such a process of paralysis as this, Jackson applies the term of dissolution.

In the case of drugs which excite nervous centres, we also notice a certain similarity of action. Thus strychnine not only causes convulsions by its stimulating action on the medulla spinalis, but stimulates also the nerve-centres for the respiration and circulation in the medulla oblongata and in the heart itself.

Action of Drugs on Motor Nerves.

The readiness with which a muscle responds to a stimulus depends both on the condition of the muscle itself, and on the terminations of motor nerves within it. A faradaic current readily stimulates the nerve-endings, but does not act at all readily on the muscle. The making and breaking of a constant current, on the other hand, has comparatively slight action on the nerves, but a powerful action on the muscle. One of the questions which arises most constantly in connection with the action of drugs is:—whether or not they paralyse the end of the motor nerves in muscle. This question was fully worked out by Bernard, and also independently by Kölliker, in relation to **curare.**

The same **methods of experiment** were adopted by both. They were twofold, and consisted:

1. In applying the poison to that part of the body alone which seemed affected by it, and seeing whether it produced its usual action.

2. In preventing it from reaching that part, and seeing whether its usual effect was then absent.

The first of these methods consisted in the local application of the drug to the muscles and motor nerves themselves (Figs. 52 and 53). The second consisted in ligaturing the artery of one leg in a frog, so as to prevent the poison from reaching the muscles and motor nerves in that leg (Fig. 54).

The advantage of the first method, viz. that of local application, is that it allows us to deal with only one organ at a time, and the results are therefore less complicated than those of the second method. In some respects it is better to begin with the second method and work back to the simpler from the more complex organs (p. 149).

Paralysis of Motor Nerve-endings.— Curare produces symptoms of paralysis. **Paralysis may be due to** the action of the drug on the **muscles** themselves, on the **motor nerves** which set them in action, or on the **nerve-centres** which originate motor impulses. In order to decide this, Bernard applied electricity to the nerves and to the muscles of a frog poisoned by curare administered subcutaneously. He thus found that when the nerve was irritated no effect was produced on the muscles; but that when the muscle itself was stimulated, it contracted readily. In order to decide whether this loss of irritability in the nerve was due to a change in the nerve-trunk, or in the terminations within the muscle, Bernard employed the first method, that of **local application.** He placed a solution of curare in two watch-glasses. In one he immersed the trunk of the nerve (Fig.

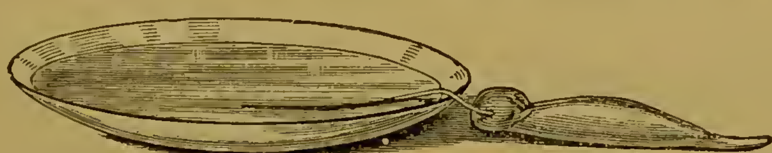

FIG. 52.—Shows the method of applying a drug in solution locally to the trunk of a nerve.

52), and in the other the muscle, so that the solution penetrating between the fibres could reach the nerve-endings (Fig. 53). He

FIG. 53.—Shows the method of applying a drug in solution locally to a muscle and the ends of motor nerves within it.

then irritated the nerve attached to both muscles, and found that irritation caused contraction readily enough in the case

where the nerve-trunk had been steeped in the solution of curare, but had no effect when the curare had been allowed to reach the nerve-ends by immersion of the muscle in the solution. The irritability of the muscle itself to mechanical stimuli, or to the making and breaking of a constant current directly applied to it, remained quite unaltered, so that the muscular fibre had evidently not been affected by the action of the poison.

The second mode of testing the action of drugs upon motor nerves, viz. that of **local protection**, consists, as has been stated, in allowing the drug to be carried to the muscles and nerve-endings

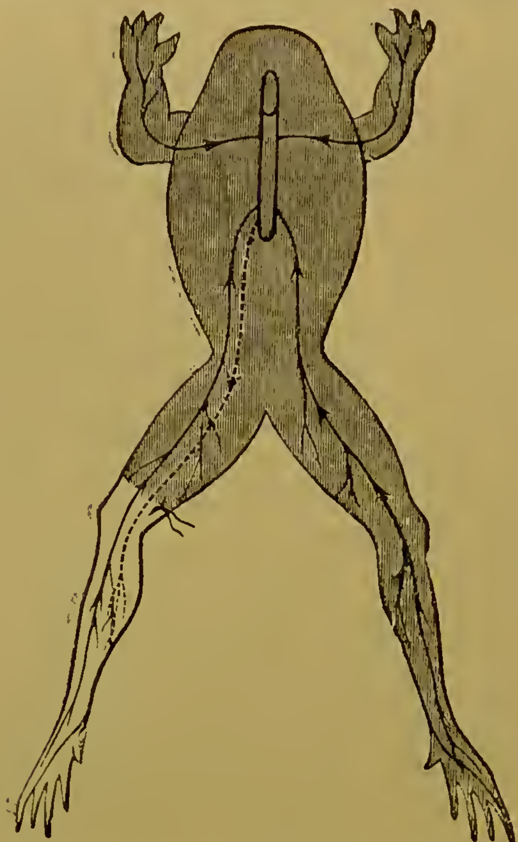

FIG. 54.—Diagram of the mode of experimenting on motor and sensory nerves in the frog.—The shaded part shows where the poison has been carried by the circulation. The unshaded left leg shows where the tissues have been protected from the poison by ligature of the artery just above the knee. The unbroken lines with arrows pointing to the spinal cord indicate the sensory nerves. The broken line with arrows pointing outwards indicates the motor nerve to the unpoisoned leg.

by the circulating blood in one leg of a frog, while it is prevented from reaching the other either by ligaturing (Fig. 54) the blood-vessels alone, or ligaturing the whole leg with the exception of the sciatic nerve. After some time has elapsed, the sciatic nerve is stimulated on each side. If the muscles of the poisoned limb do not contract at all or do so more feebly than in the unpoisoned limb, it is evident that the poison has paralysed either them or the motor nerves. In order to decide whether the nerves or the muscles are paralysed the muscle is next stimulated directly; if it then contracts normally it is evident that the paralysis observed when the nerve was irritated is due to the action of the

drug on the nerve-endings. If the muscle is completely paralysed, no definite conclusion can be drawn regarding the nerve-endings, but if the muscle shows only partial paralysis, and the paralysis is greater when the nerve is stimulated than when the muscle is stimulated directly, we conclude that the drug has acted upon both the muscular substance itself and the motor nerve-endings within it.

The effect of drugs in paralysing motor nerves is chiefly investigated in frogs as the action comes out much more distinctly in them.

Warm-blooded animals may die from paralysis of the motor nerves while the nerves still respond readily to faradaic stimuli applied to them, the faradaic stimulus being much greater than that normally sent along the nerves from the nerve-centres. Thus after an animal has been killed by paralysing it with curare, its muscles will still respond readily to electrical stimulation of the motor nerves.

A **fallacy** to be guarded against in experiments on the results of preventing a poison from reaching one part of the body is that caused by diffusion. Even when the circulation is stopped in a frog's leg by ligature of the artery, poison introduced into the dorsal lymph-sac may pass down the limb by diffusion and affect the parts below the ligature. This may be to a great extent prevented by ligaturing the whole limb *en masse*, at the same time carefully excluding the sciatic nerve from the ligature. Diffusion may also occur although the circulation has been stopped throughout the whole body by removal of the heart and other viscera, and the anterior part of the spinal cord may be affected before the posterior when the poison is injected into the dorsal lymph-sac.

Advantage of the Method of Local Protection.—The advantage of this method is that it affords information regarding the action of the poison upon other parts of the nervous system, viz. the nerve-centres and sensory nerves, as well as upon the motor nerves. It also gives the order in which the poison affects the various nervous structures, and shows whether the quantity of poison conveyed to the nerves by the circulation is sufficient to paralyse them or not. For some substances, directly applied to the ends of the motor nerves, may paralyse them, although they do not have this effect when injected into the blood: the reason being that the quantity applied to the nerves directly may be much greater than that which reaches them through the circulation.

The muscles and ends of the motor nerves being protected in the ligatured leg from the action of the poison while it still remains in connection with the nerve-centres by means of the sciatic nerve, this method serves as an index to show what is going on in the nerve-centres. Thus in a frog poisoned by

curare it is found that the ligatured leg moves on irritation of the sensory nerves, while all the poisoned parts remain perfectly still. This shows that the afferent nerves are still capable of conveying impressions to the spinal cord, and the cord itself of reflex action, although the poisoned limbs give no indication of the changes which are occurring in the nerve-centres. By-and-by irritation of a sensory nerve or root ceases to produce any movement even in the ligatured limb. This effect is shown to be due to paralysis of the nerve-centres by observing the effect of irritation of the nerves in the ligatured limb, for the muscles still respond readily to irritation of the nerve by a moderate stimulus. We may conclude with tolerable certainty that the motions have ceased in the limbs because the nerve-centres have become paralysed.

Paralysers of Motor Nerves.—Many other drugs have an action somewhat similar to that of curare upon the motor nerves:—

Ammonium cyanide.[1]
,, iodide.
Ethyl ammonium chloride.[1]
Amyl ammonium chloride.[1]
,, ,, iodide.[1]
Amyl ammonium sulphate.[1]
Phenyl-di-methyl-ethyl ammonium iodide.[13]
Phenyl-di-methyl-amyl ammonium iodide.[13]
Phenyl-di-methyl-amyl ammonium hydrate.[13]
Phenyl-tri-ethyl ammonium iodide.[13]
Tri-methyl ammonium iodide.[2]
Tri-ethyl ,, chloride.
,, ,, iodide.
,, ,, sulphate.
Methyl-tri-ethyl stibonium iodide.[14]
Methyl-tri-ethyl ,, hydrate.[14]
Toluyl-tri-ethyl ammonium iodide.[13]
Di-toluyl-di-ethyl ,, ,, [13]
Toluyl-di-ethyl-amyl ,, ,, [13]
Toluyl-tri-ethyl ,, hydrate.[13]
Tetra-methyl ,, iodide.
Tetra-ethyl ,, ,,
Tetra-methyl ,, iodide.[13]
Tetra-amyl ,, ,, [13]
Tetra-ethyl phosphonium iodide.[14]
Tetra-ethyl arsonium iodide.[14]
Tetra-ethyl arsonium and zinc double iodide.[14]
Tetra-ethyl arsonium and cadmium double iodide.[14]
Anchusa.[3]
Methyl anilin.[4]
Ethyl ,, [4]
Amyl ,, [4]
Methyl-atropine.[2]
Methyl-brucine.[2]
Ethyl-brucine.[3]
Camphor.
Methyl-cinchonine.[3]
Amyl ,, [3]
Chloroxethylene.
Methyl-codeine.[2]
Collidine.
Coniïne.
Di-methyl-coniïne.[2]
Cotarnine.[3]
Cynaglossine.[5]
Di-methyl ammonium chloride.[1]
,, ,, iodide.[1]
,, ,, sulphate.[1]
Di-ethyl ,, chloride.[1]
,, ,, iodide.[1]
,, ,, sulphate.[1]
Curarine.[6]
Curare.[7]
Ditaïne.[8]
Methyl-delphinine.[3]
Echium.[3]
Erythrina corallodendron.[9]

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[1] Brunton and Cash, *Proc. Roy. Soc.*
[2] Crum-Brown and Fraser, *Trans. of Roy. Soc. of Edinburgh.*
[3] Buchheim and Loos, Eckhard's *Beiträge*, Bd. v.
[4] Jolyet and Cahours, *Compt. Rend.*, lxvi. p. 1181.
[5] Diedülin, *Med. Centralbl.*, 1868, p. 211.
[6] Preyer, *Göttinger Ztschr. f. Chemie*, 1, p. 381.
[7] Bernard and Kölliker.
[8] Harnack, *Arch. f. exp. Path. u. Pharm.*, vii. p. 126.

Guachamachà.[10]	Methyl-piperidine.
Lobeline.	Saponine.
Methyl-morphine.[2]	Sparteine.
Methyl-nicotine.[2]	Methyl-strychnine.[2, 12]
Ethyl ,, [3]	Ethyl ,, [2]
Ptomaïnes.[11]	Methyl-thebaïne.[2]
Methyl-quinine.[3]	Methyl-veratrine.[3]
,, quinidine.[2]	Amyl ,, [3]

Although the substances mentioned in the above list have all the power of paralysing motor nerves, they do not possess the same power as curare. In the case of the salts of ammonium and the compound ammonias, the curare-like action is accompanied by a paralysing effect upon the muscular substance and on the nerve-centres. When salts of these substances are employed, their effect is somewhat modified by their acid radical, although this is not the case to the same extent in the salts of the compound ammonias, and in the salts of ammonium itself. Thus the iodide of ammonium has a much stronger paralysing action on the nerves than bromide, chloride, sulphate, or phosphate, and this is observed also, though to a less extent, in the salts of the compound ammonias.[1]

Exact Localisation of the Action of Curare.

The experiments already described have shown that curare does not paralyse the trunks of motor nerves (p. 148), nor the muscular substance (p. 148), and does paralyse the peripheral terminations of the motor nerves within the muscles: but they do not show what the exact part of the peripheral terminations is on which the drug exerts its action.

When a nerve enters a muscle it divides and subdivides dichotomously until the fibres become single, and, losing their myelin sheath, the axis-cylinders enter the muscular fibres. There they end in the nerve-plates, from which the ultimate branches pass to the muscular substance.

The paralysis produced by curare may be due to its action on:

(*a*) The single nerve-fibrillæ before they completely lose their myelin sheath;

(*b*) The axis-cylinders;

(*c*) The end plates;

(*d*) The ultimate branches.

As curare acts so much more readily on the nerves passing

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[9] Harnack, Buchheim's *Pharmacologie*, 3rd ed. p. 615.

[10] Sachs, *Archiv f. Physiol.*, 1877, p. 91: Schiffer, *Deutsch. med. Wochenschr.*, 1882, No. 28.

[11] Several authors quoted by Guareschi and Mosso, *Les Ptomaïnes*, 1883.

[12] Schroff, *Wochenblatt d. Ztschr. d. Aertze zu Wien*, No. 14, 1866.

[13] Rabuteau, *Traité élémentaire de Thérapeutique*, 4me ed. p. 536 *et seq.*

[14] Vulpian, *Arch. de Physiologie*, 1868.

to voluntary than on those passing to involuntary muscles, and the most marked anatomical difference between these two kinds of

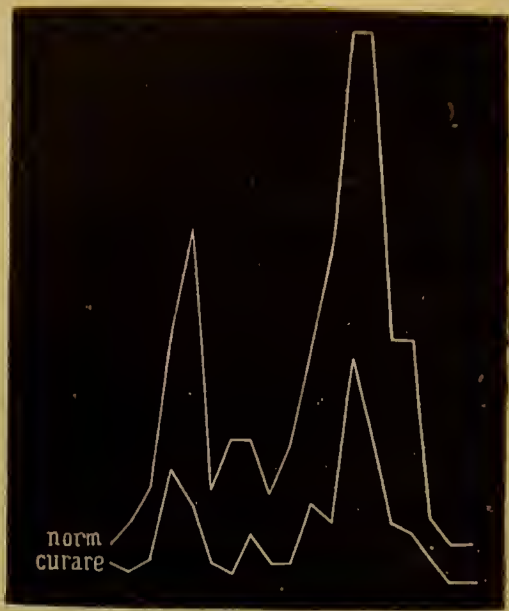

FIG. 55.—Curve showing the excitability in different parts of the sartorius of a frog in a normal and curarised muscle.

muscles consists in the termination of the former in end plates, it is natural to suppose that curare acts upon these plates.

FIG. 56.—Shows the distribution of the nerves in the gastrocnemius of the frog and the curve of excitability in different parts of the muscle. It will be observed that the excitability is greatest in those parts where there are most nerve-endings.

Moreover, this supposition appears to receive confirmation from the observation of Kühne—that the end plates undergo a certain alteration in poisoning by curare, their outlines becoming more

distinct than in the normal condition. This slightly increased sharpness of outline may be regarded as indicating a slight physical change, which might, however, be associated with such profound chemical changes in the end plates as to destroy their power of conducting stimuli from the nerve to the muscle.

But recent researches by Kühne and one of his pupils, Politzer, appear to render it probable that some of the nerve-structures within the muscle retain their functional activity even in profound poisoning by curare; and Politzer supposes that the part of the nerve which is acted on by curare is the nerve-fibril before it has quite lost its medullary sheath, and that the poison destroys the conducting power of the nerve by acting on the cement-substance at Ranvier's nodes. The grounds on which this supposition is based are that, even in profound poisoning by curare, those parts of the sartorius of the frog which contain nerve-endings are more irritable than those which contain none (Fig. 56), and that the irritability increases or diminishes in proportion to the number of nerve-endings, just as it does in the normal muscle, although the excitability of all the parts containing nerves is less than normal in curare-poisoning.

That this variation in irritability in different parts of the muscle is due to nervous structures, and not to variations in the muscular fibres themselves, is shown by the fact that, when the excitability of the nerve is depressed by throwing it into a state of anelectrotonus, these variations in the excitability of the muscle disappear.

It is just possible that the nervous structures which retain a certain amount of excitability in curare-poisoning may be the ultimate terminations which pass from the motor plate to the muscular fibre: but Politzer appears to throw this possibility aside, and considers that the amount of nervous excitability retained shows that all the parts beyond the last node of Ranvier still possess their functions.

Should Politzer's supposition—that curare paralyses motor nerves by acting on the cement at Ranvier's nodes—be correct, it may perhaps serve to explain, not only the difference between its action on motor nerves going to voluntary and those going to involuntary muscular fibre, but also the difference between the action of curare, or poisons having a similar action, and of atropine on the inhibitory fibres of the vagus.

Action of Drugs in Increasing Excitability of Motor Nerves.

It is not so easy to prove positively that a drug has increased as that it has diminished the excitability of motor nerves. The fact that the nerves of the poisoned leg are found to be more excitable than those of the ligatured one in such experiments as those just described, does not prove it, for it must be borne in

mind that the arrest of the circulation in the ligatured leg lessens the excitability of the muscles and the nerves in it. This effect of the ligature strengthens the proof that a drug has produced paralysis when we find that, in spite of the freer circulation, the poisoned leg is less irritable than the ligatured one; but it prevents our concluding that the drug has increased excitability when we find that the poisoned leg responds more readily to stimuli than the ligatured one.

To try whether a drug increases excitability we treat two muscles with saline solution, and after ascertaining that their excitability is alike we add the drug to be tested to the saline solution in which one muscle is steeped, and after some time test the excitability again. If the muscle in the poisoned saline solution becomes more excitable than the other, we conclude that the increase is due to the action of the drug.

Irritation of Motor Nerve-endings by Drugs.—The peripheral terminations of motor nerves in muscle appear to be irritated by certain poisons, so that the excised muscle exhibits fibrillary twitchings. This might be due to irritation of the muscular structure itself, but as they are gradually abolished by curare they are supposed to depend upon irritation of the terminations of motor nerves. The poisons which produce this effect are: aconitine, camphor, guanadine, nicotine, pilocarpine, pyridine. Physostigmine produces it most markedly in warm-blooded animals, but does not seem to cause it in frogs.

Action of Drugs on the Trunks of Motor Nerves.—Nerve-trunks are, as a rule, very much less affected by poisons than the end-plates; but they may, nevertheless, be also acted upon by strong solutions of a poison. It appears necessary to apply the poison locally to them, and they are probably little if at all affected by poisons introduced into the system generally. The action of poisons is tested by placing a small piece of gutta-percha tissue under the nerve-trunk, usually the sciatic of the frog, and applying the poison directly to it, or dipping the nerve into a weak solution of common salt, or of sodium phosphate, to which the poison has been added, and comparing the poisoned nerve with one dipped into a similar saline solution without the poison.

There are two methods of comparison. The first consists in using the contraction of the corresponding muscle as an index of the functional power of the nerve; the second in ascertaining the effect of the poison on the normal electrical current in the nerve.

The motor fibres of a nerve appear to have their excitability abolished more readily than that of sensory nerves by changes in the body generally, and sometimes also by the local application of drugs to them. Thus in wounded nerves the motor function may be destroyed, while the sensory function is little altered,

and where both sensibility and motion have been destroyed by a bruise of the nerve-trunk, the sensibility may reappear, while the motor power does not. In rheumatic neuralgia there is not unfrequently motor paralysis with exaggerated sensibility. When a solution of physostigmine is applied locally to the nerve-trunk for a while, and the nerve is then irritated beyond the point of application, it is found that it will produce reflex movements of the body after it has ceased to do so in the limb supplied by the nerve, which shows that the sensory fibres can still conduct impressions, though the motor fibres cannot. Longer application of the poison will destroy the sensory fibres also. When a paste of theine is applied to the sciatic nerve, or the nerve is dipped in a solution of opium, similar results are observed.

By dipping nerves in a solution of the poison Mommsen finds that atropine diminishes the irritability of the nerves, affecting first the intramuscular endings, and afterwards the trunks. Alcohol, ether, and chloroform first increase and then diminish the irritability.

Action of Drugs on Sensory Nerves.

The general action of a drug on sensory nerves is much more difficult to ascertain with precision than its effect upon motor nerves, because the evidences of sensation we have in the lower animals are cries, and movements either of the limbs or involuntary muscles, such as the iris, arteries, or bladder, which ensue on irritation of sensory nerves.

In the production of these movements or cries, many structures are concerned, viz. sensory nerves, nerve-centres, spinal or cerebral motor nerves, and muscles. It is comparatively easy to ascertain the local action of the drug upon sensory nerves, for in this case these other structures are not affected. By applying the substance to one part of the body, either by painting it upon, or injecting it under, the skin, and then comparing the effect of stimulation produced by pinching or by the application of heat or electricity upon that and other parts of the surface, we can see whether or not the sensibility of the sensory nerves has been affected by the drug.

But when the drug is absorbed into the circulation, it may affect all the other structures already mentioned, as well as the sensory nerves, and thus it may be impossible to decide with certainty whether these nerves are affected or not. But even here definite results are sometimes obtainable, as in the case of curare. The method of experimenting is that of local protection, arresting the circulation in one leg of a frog by applying a ligature to the sciatic artery. The animal is then poisoned with curare, or any drug the action of which is to be ascertained. The poison is carried by the circulation to all other parts of the body excepting the ligatured leg.

In the case of curare the motor nerves are paralysed by the drug, and it would be impossible to ascertain whether irritation of the sensory nerve produced any effect at all, were it not that the ligatured limb, retaining its irritability, serves as an index to the condition of the nerve-centres. At first it is found that pinching the poisoned foot will cause movements in the non-poisoned leg. This shows that the sensory nerves retain their irritability and transmit the stimulation up to the spinal cord, whence it is reflected down the motor nerves to the non-poisoned foot.

As the poisoning becomes deeper, however, pinching the poisoned leg produces much less effect.

This might be due to paralysis of the spinal cord, but it is shown that this is not the case by pinching the ligatured leg just above and below the ligature.

It is found that a pinch just below the ligature causes marked reaction, while a pinch just above has little or no effect.

In this experiment all the structures concerned in the movement have been alike subjected to the action of curare with the exception of the ends of the sensory nerves below the ligature. It is thus evident that the diminished reaction from pinching above the ligature is due to paralysis of the ends of the sensory nerve, in the part of the body to which the poison has had access, and which is shaded dark in the engraving (Fig. 54).

In the experiment just mentioned, the second of the two methods already described (p. 147) in the reference to motor nerves is employed, and the action of the drug on the ends of sensory nerves is ascertained by preventing the poison from reaching them; but the first method may also be employed and the action ascertained by applying the poison to the ends of the sensory nerves, while the nerve-trunks and nerve-centres are protected from its action. Thus, in the experiments of Liégeois and Hottot upon the action of aconitine on the sensory nerves, they ligatured the vein and injected the poison into the artery of a frog's leg; the poison was thus carried to the ends of the sensory nerves in the skin, while it was prevented from reaching the nerve-centres. In this way they found that irritation of the poisoned skin ceased to produce any reflex action, while stimulation of the trunk of the nerve distributed to that leg still caused well-marked reflex action. Normally the terminations of a sensory nerve in the skin are much more sensitive than the trunk of the nerve; and this experiment therefore proves that aconitine paralyses the ends of the sensory nerves.

The local action of drugs on the sensory nerves in man is ascertained by producing, when applied locally, either diminution in pain which may be present at the time, or insensibility, which is usually ascertained by the æsthesiometer. This instrument is simply a pair of compasses with blunt points and a scale

by which the distance of the points from one another can be read off.

When the sensation is acute, the points are distinctly felt as two, even when they are but slightly separated from one another; but when the sensation is blunt, they are felt as one when they are at a considerable distance apart.

In frogs the local action on sensation is ascertained by dipping one leg for some time in the solution to be tested, and then comparing the effect of irritating corresponding points in the two feet or legs by pinching, by the application of acids, or by a faradaic current. In this way it has been ascertained that hydrocyanic acid has a powerful local action in paralysing sensory nerves. Where the drug is very powerful, its action on the nerve-centres might complicate the result, if a sufficient quantity should be absorbed into the blood. This fallacy may be avoided by arresting the circulation entirely through excision or ligature of the heart.

Local Sedatives and Local Anæsthetics.—Local sedatives are substances which diminish, and local anæsthetics are substances which destroy, the sensibility of the skin for the time being.

Local Sedatives.	Local Anæsthetics.
Aconite.	Extreme cold.
Atropine.	Ice.
Belladonna.	Ether spray.
Carbolic acid.	Carbolic acid.
Chloroform.	Cocaine.
Chloral.	Kawa-resin.[1]
Morphine.	
Opium.	
Veratrine.	

Action.—Their effect in some degree is due to a paralysing action upon the terminal branches of the cutaneous nerves. It is probably, to some extent, also due to an effect upon the vessels and tissues analogous to that which is produced by rubbing or scratching, which, as everyone knows, gives temporary relief to itching. Sweating also relieves the itching, which is sometimes felt just before it begins.

Uses.—Local sedatives are employed to relieve itching and to lessen pain, whether it be due to neuralgia or inflammation. Local anæsthetics are employed temporarily to abolish the sensibility of the skin, and allow slight incisions or operations to be made painlessly.

Stimulating Action of Drugs on the Peripheral Ends of Sensory Nerves.—The peripheral terminations of sensory nerves appear to become more sensitive when the supply of blood

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[1] Lewin, *Ueber Piper methysticum (Kawa)*. Berlin, 1886.

to the part is increased. This is markedly seen, not only in inflammation, where the part becomes exceedingly tender, but in cases where turgescence of the vessels occurs under physiological conditions. Besides the class of irritants which act on the peripheral terminations of sensory nerves so as to cause pain when locally applied, there are several drugs which appear to have a special irritant action on the ends of sensory nerves when introduced into the circulation: these are aconite and aconitine, which give rise to a peculiar tingling and numbness in the tongue, lips, cheeks, and indeed in all parts supplied by the fifth nerve. Veratrine also causes peculiar sensations in the sensory nerves when taken internally, but these are felt more in the fingers and toes, and in the joints, than in the tongue.[1]

[1] Von Schroff, *Pharmacologie*, 4th ed. p. 584.

CHAPTER VII.

ACTION OF DRUGS ON THE SPINAL CORD.

In the spinal cord we have to distinguish three functions: that of **conduction**, that of **reflex action**, and that of **origination** of nerve-force, as in the sweat-centres, &c., contained in it.

The spinal cord **transmits** sensory or afferent impulses **upwards** to the medulla and brain; and motor impulses **downwards** to the muscles, as well as other efferent impulses to the glands. It transmits reflex impulses **across**, either from behind forwards, or laterally from one half of the cord to the other. Transmission from behind forwards occurs when the impulse passes from the sensory to the motor columns on the same side, as in the case of reaction of a sensory stimulus on the same side of the body. It occurs laterally when the sensory stimulus produces motion, not on the same side, but on the opposite side of the body.

Action on the Conducting Power of the Cord.—Its **conducting** power for **motor** impulses is assumed to be impaired when it is noticed that any drug causes partial paralysis of the hinder extremities of an animal before the anterior extremities.

It is usually tested by irritating the spinal cord at its upper end, either mechanically with the point of a needle, or by a galvanic or faradaic current passed through electrodes inserted into it close together, and observing whether irritation of the cord itself in this way causes contraction in the muscles of the legs.

When no contraction is produced by irritation of the cord itself, while direct irritation of the motor nerves can still produce vigorous contraction, it is evident that the cause of the paralysis must be that the spinal cord has lost its power to conduct motor impulses.

These experiments may be made in a frog, the cerebrum of which has been previously destroyed; and they may be confirmed in warm-blooded animals where sensibility has been destroyed by a section of the cord, just below the medulla, and respiration is kept up artificially. The spinal cord is then exposed, and the anterior columns are irritated in the ways already mentioned.

The power of the cord to **conduct sensory impressions** is ascertained by exposing it under anæsthetics and allowing their influence to pass so far off that the animal is capable of giving

evidence of sensation. The posterior roots are then irritated before and after the injection of the poison into the circulation.

When it is found that after the poison is injected the irritation of the posterior roots which previously caused evidence of sensation no longer produces any effect, while irritation of the anterior columns still produces motion, the conclusion appears to be just, that the poison has paralysed the conducting power of the sensory columns of the cord.

This action appears to be possessed by caffeine, for Bennett found that while irritation of the posterior roots of the cord caused violent struggles and loud cries in a rabbit before the injection of caffeine into the circulation, similar irritation, after the injection, caused only a slight quiver. That this effect was not due to motor paralysis was shown by the fact that irritation of the anterior columns caused violent muscular contractions after the injection as well as before it.[1]

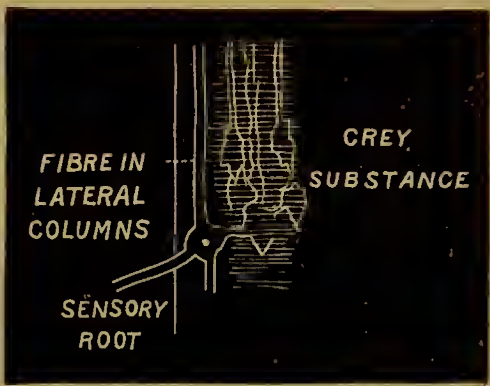

FIG. 57.—Diagram to show the effect of chloroform, chloral, and other anæsthetics on conduction of painful impressions in the spinal cord.

Ordinary impressions of touch, temperature, and muscular action are transmitted through the posterior roots of the spinal cord to the ganglia of the posterior horn of the grey substance, and thence upwards by the fibres of the lateral columns. Painful sensations, however, appear to be transmitted upwards through the grey substance of the cord. The afferent nerves, which transmit impressions from one part of the cord to another, so as to produce co-ordinated reflex movement, are contained in the posterior columns of the cord.

It is evident that any injury or poison which chiefly affects the grey matter so as to diminish its conducting power may abolish pain while reflex action still persists. This condition may be produced by division of the grey matter of the cord, and it occurs also at a certain stage of the action of anæsthetics such as chloroform and ether.

The action of drugs on the power of the spinal cord to **conduct reflex stimuli** both transversely and longitudinally has been carefully investigated by Wundt. He first ascertains the

[1] Hughes-Bennett, *Edin. Med. Journ.*, Oct. 1873.

time which elapses between the application of a stimulus to a motor nerve and the contraction of a muscle, the nerve used being the sciatic, and the muscle the gastrocnemius of a frog. This time, which includes that requisite for the stimulus to travel down the motor nerve and to set the muscle in action, he terms the **direct latency.** He next stimulates a sensory root of the spinal nerve at the same level and on the same side as the motor nerve, taking care that the stimulus does not act on the motor nerve directly, but only reflexly through the cord. The time between the application of the stimulus and the commencement of contraction he terms the **total latency.** By deducting the direct latency from the total latency, he ascertains the time required for the stimulus to pass through the grey matter of the cord from the posterior to the anterior horn of the same side. This he calls the **reflex time.**

The time required for **transverse** conduction is ascertained by applying the stimulus to a posterior root on the other side and comparing the latency with that of stimulation to a posterior root on the same side.

The time required for **longitudinal** conduction is ascertained by applying a stimulus to the brachial nerve, so that it has to travel down the greater part of the length of the spinal cord before it can excite the sciatic nerve. By comparing the latent

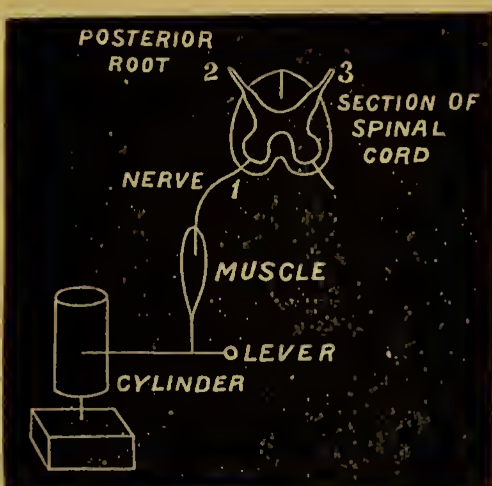

FIG. 58.—Diagram to show the method of investigating reflex and transverse conduction in the spinal cord. The motor nerve is first irritated at 1. As the cylinder revolves at a known rate, and a mark is made upon it by an electro-magnet at the instant the nerve is irritated, the distance between this mark and the commencement of the muscle curve indicates the time required for the irritation to travel down the motor nerve to the muscle and set it in action. The irritation is next applied to the posterior root on the same side (2). The distance between the commencement of contraction in this case and in that where the motor nerve was irritated gives the time required for simple reflex transmission of the stimulus from the posterior to the anterior horn of the cord. The stimulus is then applied to the posterior root on the opposite side at 3, and the distance between the commencement of the consequent contraction and that of the curve obtained by irritating at 2 gives the time required for transmission across the cord.

period of excitation in the brachial nerve with that of the sciatic on the same side[1] the length of time required for longitudinal

[1] For convenience sake both the sciatic and the brachial nerves are taken in this experiment on the opposite side from the muscle, so that the time of longi-

transmission of stimuli in the cord is ascertained. The mode of ascertaining the time of ordinary reflex and transverse transmission in the cord is shown diagrammatically in Fig. 58.

The differences in the latent period and in the form of the muscle curve obtained by irritation of the motor nerve, and by simple transverse, and longitudinal reflex stimulation, are shown diagrammatically in Fig. 59. Wundt found that when a motor

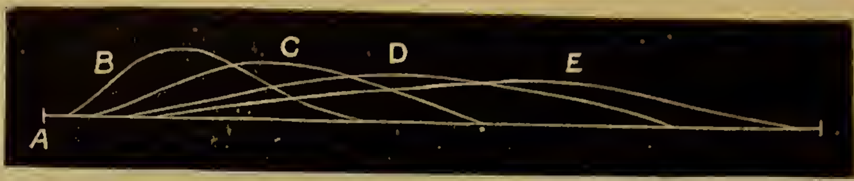

FIG. 59.—Diagram to show the difference between the length of the latent period and form of the curve in contraction induced, B, by direct irritation of the motor nerve; C, by simple reflex from irritation of the cord on the same side; and D, by cross reflex from irritation of the cord on the opposite side to that from which the motor nerve proceeds, as shown in Fig. 58. E shows combined transverse and longitudinal reflex; A indicates the moment at which the stimulus was applied in each case.

nerve was irritated at a point distant from the muscle the resulting contraction had not only a longer latent period, but was less in height and longer in duration than when the nerve was irritated close to the muscle. From a comparison of the curves it will be seen that a **small portion of grey matter** has a **similar effect** upon the stimulus which passes through it that a **great length of nerve-fibre** would have. In all reflex actions, therefore, in the normal animal, the contraction of the muscle has a longer latent period, less height, and longer duration than that produced by direct irritation of the motor nerve. The increase in the latent period, diminution in height, and longer duration are greater in the case of transverse than of simple reflex, and greater still in the case of combined transverse and longitudinal reflex.

In the normal frog a stronger stimulus is necessary to produce reflex contraction than would be sufficient if it were applied directly to the motor nerve, and strong and weak stimuli will produce strong and weak muscular contractions. The spinal cord has a power of **summation** similar to that already referred to in the case of contractile tissue of medusæ, so that a stimulus which would be powerless to produce a reflex contraction if applied once to a posterior root or to a sensory nerve will be effectual if repeated several times in close succession.

Strychnine has an effect on the conducting power of the spinal cord which we should hardly expect, and so have other convulsant poisons. It increases the excitability so much that slighter stimuli than before will produce reflex action, and it destroys to a considerable extent the power of summation, so that instead of each stimulus producing a contraction in propor-

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tudinal conduction is ascertained by deducting the transverse from the combined transverse and longitudinal conduction.

tion to its strength, all have the same effect—a weak one, which is just strong enough to produce an effect at all causing as great a contraction as the most powerful. The time required for the transmission of stimuli through the cord is enormously increased, so that the latent period of ordinary reflex, and still more of transverse and longitudinal reflexes, is greatly increased, sometimes, indeed, to as much as ten times the normal. The retardation of transverse conduction is not absolutely greater than of longitudinal conduction ; but, as the distance through which the stimulus has to pass in the former case is much less than in the latter, it follows that strychnine increases the resistance more transversely than longitudinally. Morphine in small doses has no very marked action upon the cord, but larger doses have an action almost exactly like that of strychnine, causing increased reflex irritability, tetanic contractions, and prolonged latency. Veratrine has a similar action. Nicotine and coniïne in small doses have a similar action to strychnine, but this is quickly masked by the rapid appearance of paralysis. When large doses are used, paralysis occurs almost immediately, and is usually accompanied by fibrillary twitchings. Atropine has at first an action similar to strychnine in causing increased excitability, prolonged latency, and tetanic contraction. It differs from strychnine in causing more rapid diminution in the irritability of the grey substance of the spinal cord and in diminishing the conducting power of peripheral nerves. In consequence of this, irritation of the sciatic nerve in a frog poisoned by atropine causes two contractions, one direct and one reflex, separated from each other by a distinct interval, whereas, in a frog poisoned by strychnine, these two contractions begin almost at the same moment and appear superimposed upon each other.[1]

Effect of Drugs on the Reflex Action of the Cord.—The effect of drugs upon the reflex action of the spinal cord is usually estimated by the time which elapses between the application of a stimulus and the occurrence of reflex action, before and after the administration of a drug. Longer time indicates diminished, and shorter time increased, excitability of the cord.

Method of Experimenting.—Since the spinal cord in mammals quickly loses its excitability when deprived of oxygenated blood (as shown by Stenson's experiment, p. 164), frogs are used for experiment. The method usually employed is called Türck's method. The cerebral lobes in a frog are destroyed, and after sufficient time has elapsed to allow it to recover from the shock, it is suspended either by the head or fore-legs, so that the hind-legs hang down. A very dilute solution of sulphuric acid, the acid taste of which can be little more than perceived by the tongue, is put in a small beaker and raised until one foot of the frog is completely immersed in it.

[1] According to W. Stirling, the latent period of reflex action in the spinal cord is increased by the chloride and bromide of potassium and ammonium, by lithium salts, and by chloral and butyl-chloral ; it is decreased by the chloride, bromide, and iodide of sodium.—*Stirling and Landois' Physiology*, 2nd ed., vol. ii. p. 909.

The time is then counted by means of a metronome, between the immersion of the foot in the acid solution and the time when the leg is drawn up out of it. As soon as the foot is drawn up, the acid is carefully washed off with some fresh water in order to prevent any injury to the skin, and after a minute or two, the experiment may be repeated. When the time seems constant the drug is injected into the lymph-sac, and the experiment is repeated again. The greater or less time which is required for the withdrawal of the foot from the acid after the injection of the poison, as compared with the time required before, shows the extent to which the reflex action of the spinal cord has been diminished or increased by the poison.

Direct, Indirect, and Inhibitory Paralysis of the Spinal Cord by Drugs.—When it is found that the reflex action of the cord is greatly diminished or apparently entirely abolished, it must not be at once concluded that this is necessarily due to the **direct** paralysing action of the drug itself upon the nervous substance of the cord. This may be the case, and is so when methyl-coniïne is employed, but it may be due to the **indirect** action of the drug upon the heart, weakening the circulation, and lessening the function of the cord by interfering with its blood-supply.

In order to ascertain whether this is the case or not, it is usual to take two frogs as nearly alike as possible, to destroy the brain in each, and after waiting until they have recovered from the immediate shock of the operation, to inject into one the drug to be tested, and, at the moment when it stops the beating of the heart, to tie a ligature around the heart of the other. The persistence of reflex action is then tested in the usual manner, and if it is found that it disappears much sooner in the poisoned frog than in the other one in which the heart has been ligatured, it is concluded the drug has paralysed the substance of the cord itself.

Indirect Paralysis.—The spinal cord is very rapidly paralysed in mammals if the blood-supply to it is stopped. This is readily shown by Stenson's experiment of gently compressing the abdominal aorta in a rabbit with the thumb or finger, so as to arrest the circulation for four or five minutes. On releasing the animal its hinder extremities are found to be paralysed, and this paralysis, though it may be partly due to interference with the blood-supply of the muscles and nerves of the lower extremities themselves, is chiefly due to the arrest of circulation in the spinal cord. The spinal cord in frogs is less rapidly affected, but if the circulation be arrested for half an hour or so symptoms of paralysis usually begin to appear, the time varying, however, with the temperature and other conditions. Indirect paralysis is produced by aconitine, digitalin, and large doses of quinine, which arrest the circulation. It is frequently difficult to decide how far paralysis is due to the action of a drug on the circulation, and how far to its direct action on the spinal cord itself.

Direct Paralysis.—Paralysis of reflex movement is produced by a number of substances, some of which produce little or no previous excitement; others, however, markedly increase the excitability of the spinal cord first, and are thus classed as spinal **stimulants**.

Spinal Depressants.—The following drugs belong to this class :—

Depress without marked previous excitement.	Excite first and afterwards paralyse.
Antimony.	Ammonia.
Emetin.	Apomorphine.
Ergot.	Alcohol (through circulation.
Hydrocyanic acid.	Arsenic.
Methylconiïne.	Camphor.
Saponine.	Morphine group.[1]
Physostigmine.	Carbolic acid.
Turpentine.	Chloral.
Zinc.	Nicotine.
Silver.	Potassium salts.
Sodium.	Veratrine.
Lithium.	Mercury.
Cæsium.	
Alcohol group[1] (action on nervous substance).	

Uses of Spinal Depressants.—Such substances as morphine, chloral, &c., which diminish the conducting power of the grey matter of the cord for painful impressions, are useful as anodynes, though their action in lessening pain is probably often due to their effect on the brain as well as on the spinal cord. Spinal depressants which lessen reflex action are employed in diseases where there seems to be increased excitability of various parts of the cord, as evidenced by spasm, either tonic or clonic. They are therefore employed in tetanus, trismus neonatorum, chorea, writer's cramp, and paralysis agitans. The pathology of many nervous diseases is imperfectly known, and as the action of spinal depressants is frequently a complex one of combined stimulation and depression, some of the drugs included in this class are used in paraplegia due to myelitis, locomotor ataxy, and general paralysis.

They are also used as antagonists in cases of poisoning by spinal stimulants like strychnine.

Inhibitory Paralysis. — The higher parts of the nervous system have the power of lessening the action of the lower, and in the frog this power seems to be especially marked in the optic lobes. Irritation of these either mechanically by a needle, chemically by a grain of salt laid upon them, or electrically, will lessen or entirely abolish the reflex action in the cord; but this again returns when the irritation is removed, or when its influence is destroyed by cutting the cord across, below the point of irritation. This fact was discovered by Setschenow, and thus parts of the

[1] Schmiedeberg, *Arzneimittellehre*, p. 34.

optic lobes concerned in this inhibitory action are known as Setschenow's centres.

An inhibitory action appears to be exerted by the cranial centres in higher animals also, for McKendrick observed that on decapitating a pigeon the body lies comparatively still for a second or two, and then violent convulsions set in. If the body be held firmly during these convulsions, and a moderately strong faradaic current be applied to the upper part of the spinal cord, the convulsions may be altogether arrested while it continues, again commencing when it stops. In this experiment the application of the current to the cut end of the cord is regarded as supplying a stimulus in place of that which would normally pass downwards from the brain.

Quinine causes great depression of reflex excitability, and this was stated by Chaperon to be due to the action of the drug on Setschenow's centres.

FIG. 60.—Nervous system of a frog, showing the cerebral and optic lobes, the medulla oblongata, and the spinal cord with nerve-roots. The brain is shown on a larger scale at p. 184.

Almost immediately after injection of quinine into the dorsal lymph-sac, the reflex excitability of the frog becomes very greatly reduced or almost entirely abolished, but if the spinal cord be now cut across at its upper part just below the medulla oblongata, the reflex excitability becomes as great, or even greater, than the normal.

This loss of excitability has been ascribed by Binz to the action of quinine on the heart, causing weakening of the circulation, and thus indirectly producing paralysis of the cord. This kind of paralysis does occur with large doses and after considerable time, but it is quite different from the inhibitory paralysis described by Chaperon, which comes on almost immediately after the injection of the drug into the lymph-sac, and disappears immediately on section of the cord below the medulla.

I have repeated Chaperon's experiments, and can fully confirm their accuracy. In doing so, however, it struck me that the result was most marked when a solution of quinine was concentrated and somewhat strongly acid. It therefore appeared probable that the inhibition was not due to the direct action of the quinine upon Setschenow's centres after it had been carried to them by the blood, but only to its reflex action upon them. It irritates locally the sensory nerves of the lymph-sac into which it is in-

jected, and this stimulus being transmitted to the optic lobes excites them so that they produce inhibition of that reflex action which would usually occur in the cord when the foot is irritated by acid. On testing this hypothesis by injecting acid alone into the lymph-sac, Mr. Pardington and I found that it also caused reflex inhibition like that produced by quinine. We may therefore conclude that there is nothing special in the action of quinine upon the inhibitory centres; it merely acts like other irritants on sensory nerves.[1] Probably digitalis and sanguinaria also act in a similar way.

NATURE OF INHIBITION.

Inhibition and the action of drugs on inhibitory centres play a very important part indeed in pharmacology, and on the present hypothesis they are very puzzling.

By inhibition we mean the power of restraining action which some parts of the nervous centres possess. At present it is usually supposed that certain parts of the nerve-centres, instead of having a sensory or motor function, have an inhibitory one peculiar to themselves. It is found, however, that inhibitory powers are not confined to Setschenow's centres, already mentioned (p. 166), but that almost any part of the nervous system may have an inhibitory action on other parts, so that it becomes almost necessary to abandon the old hypothesis. It is found, for example, that not only is reflex action more active in the frog when the optic lobes are removed, but that when the spinal cord is taken away in successive slices from above downwards, the reflex action in the part below goes on increasing. On the old hypothesis we are almost obliged to assume that each nerve-cell has two others connected with it, one of which has the function of increasing or stimulating, and the other of inhibiting its action. Most of the phenomena which we find can be explained in a much simpler way by supposing that nervous stimuli consist of vibrations in the nerve-fibres or nerve-cells, just as sound consists of vibrations.

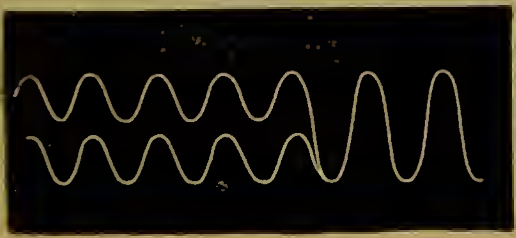

FIG. 61.—Diagram to show increased intensity of vibration by coincidence of waves.

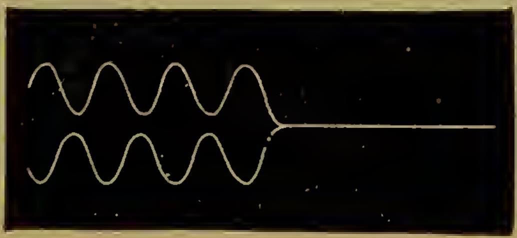

FIG. 62.—Diagram to show abolition of vibration by interference of waves.

Interference.—In the case of both sound and light we find that if two waves should fall upon one another so that their crests

[1] *St. Bartholomew's Hospital Reports*, 1876, p. 155.

coincide, the intensity of the sound or light is increased (Fig. 61), while if they fall on each other so that the crest of one wave fills up the trough of the other, they interfere so as to destroy each other's effect (Fig. 62); and thus two sounds produce silence, or two waves of light darkness. This is shown in the case of sound by a tube (Fig. 63), which divides into two branches, and these again re-unite. The length of one branch may be altered at

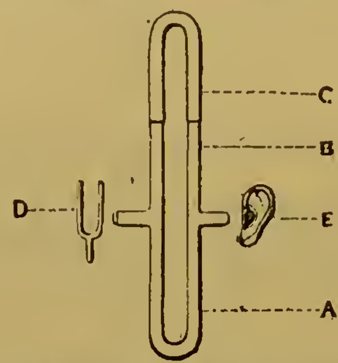

FIG. 63.—Diagram of apparatus for demonstrating the interference of waves of sound. A and B, branches of a tube; C, sliding piece by which the branch B can be lengthened or shortened at will; D, tuning-fork; E, the ear.

will, so that the sound travelling through one branch has further to go than the other. It may thus be retarded so far as to throw it half a wave-length behind the other, and silence is produced. If lengthened still further, so as to throw the one sound a whole wave-length behind the other, the crests again coincide, and the sound is again heard. Increasing the length still further, so that the one sound is thrown a wave-length and a half behind the other, they again interfere, and silence is again a second time produced. This may be repeated *ad infinitum*, silence occurring whenever the one sound falls behind the other by an odd number of half wave-lengths.

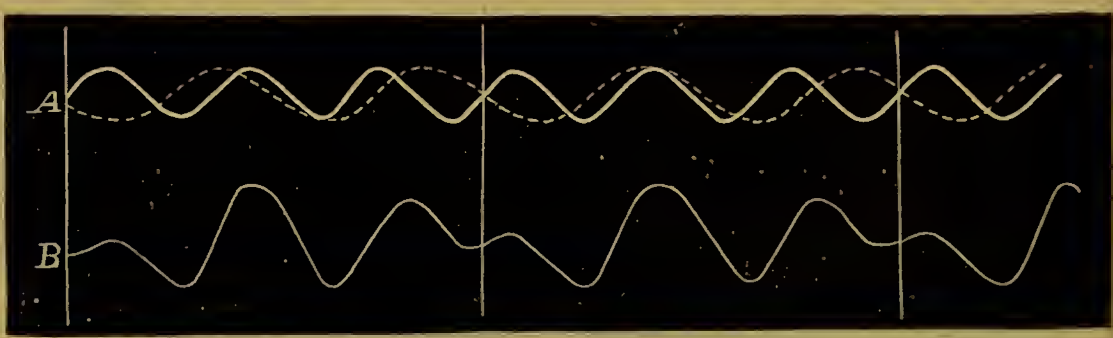

FIG. 64.—Diagram showing the beats or alternate increase and diminution of the wave-heights by the interaction of two systems of waves of different wave-lengths. At A, two systems, having a relation to each other of 3 to 1, are indicated separately by dotted and complete lines. At B the resultant of the interaction of the two systems is shown. With such a relation as that shown in the diagram, and with those of a vibrating rod generally, such as n, 3n, 5n, &c., the interference of the systems is not complete, and silence cannot be produced by the interference of sounds. (From Ganot's *Physics*.)

In the case just mentioned, the waves are of the same length, but if they are of different lengths, instead of constantly rein-

forcing and interfering with others, they may sometimes strengthen and sometimes weaken each other. The result is more or less rhythmical increase and diminution of action, or as it is termed 'beats.' This is shown in the accompanying diagram (Fig. 64).

Instances of rhythm occur in the body, which strongly remind us of this condition; for example, the different rhythms of the heart under various conditions.

Interference in Nervous Structures.—Supposing nervous stimuli to consist of vibrations like those of light or sound, the action which any nerve-cell would have upon the others connected with it would be stimulant or inhibitory according to its position in relation to them. If its relation be such that a stimulus passing from it to another cell will there meet with a stimulus from another quarter in such a way that the waves of which they consist coincide, the nervous action will be doubled; but if they interfere the nervous action will be abolished. If they meet so as neither completely to coincide nor to interfere, the nervous action will be somewhat increased, or somewhat diminished, according to the degree of coincidence or interference between the crests of the wave.

Thus if the relations of the nerve-cells S, S′ and M, M′ in the diagram (Fig. 65) are such that when a stimulus passes from a

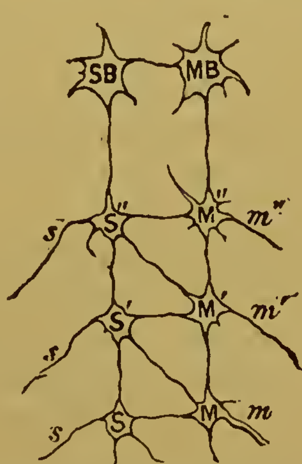

FIG. 65.—Diagram to illustrate inhibition in the spinal cord. *s*, *s′*, and *s″* are sensory nerves, *m*, *m′*, and *m″* are motor nerves, S, S′, and S″ are sensory cells, M, M′, and M″ are motor cells in the spinal cord, SB is a sensory, and MB a motor cell in the brain.

sensory nerve *s* to a motor nerve *m*, one part of it travels along the path *s*, S, M, *m*, and another along *s*, S, S′, M, *m*, or *s*, S, S′, M′, M, *m*, at such a rate that the crests of the waves coincide at the motor cell M, they will increase each other's effect. If they interfere, the effect of both will be diminished or destroyed, i.e. inhibition will occur.

Effect of Altered Rate of Transmission.—But it is evident that the coincidence or interference of nervous stimuli travelling along definite nerve-paths, will vary according to the rate at which they travel, so that when stimuli which ordinarily interfere with one another, are made to travel more slowly, one may be

thrown a whole wave-length, instead of half a wave-length, behind the other: and thus we get coincidence and stimulation, instead of interference and inhibition. When stimuli, whose waves ordinarily coincide and strengthen each other's action, are made to travel more slowly, one may be thrown half a wave-length behind the other, and thus we shall have interference and inhibition instead of stimulation.

On the other hand, when the stimuli travel more quickly, the one which was half a wave-length behind the other, and interfered with it, may be thrown only a small fraction of a wave-length behind it. It will thus, to a great extent, coincide and cause stimulation, while the one which normally coincides with and helps another may, by travelling with increased rapidity, get half a wave-length in front of the other, and cause inhibition.

Opposite Conditions produce Similar Effects.—We see then that results, apparently exactly the same, may be produced by two opposite conditions, increased rapidity or greater slowness of transmission of stimuli.

The Same Conditions may cause Opposite Effects.—We see also that the same conditions may produce entirely opposite effects, by acting more or less intensely. Thus, the application of cold, or of any agent which will render the transmission of stimuli along nervous channels slower than usual, may throw one which ordinarily coincided with another a small fraction of a wave-length behind it, then half a wave-length, then three-quarters, next a whole wave-length, and then in addition to the whole wave-length it will throw it, as at first, a small fraction or a half wave-length behind, and so on.

We shall thus have the normal stimulation passing into partial, then into complete inhibition, which will gradually pass off as the crests of the waves come more nearly together, until they coincide, when we shall again have stimulation as at first. As the action proceeds, this second stimulation will again pass into inhibition. In the same way a gradual retardation of transmission will cause impulses, which normally interfere, gradually to coincide until inhibition gives place to complete stimulation, and this again passes into inhibition. By quickening the transmission and throwing one wave more or less in advance of another, various degrees of heat will likewise produce opposite effects.

Stimulation and Inhibition on this Hypothesis are merely Consequences of Relation.—Stimulation and Inhibition are not due to any particular stimulating or inhibitory centres; they are merely dependent on the wave-length of nervous stimuli or the rapidity of transmission, and on the lengths of the paths along which they have to travel. Any nerve-cell may therefore exercise an inhibitory or stimulating action on any other nerve-cell, and the nature of this action will be merely a question of

the length and arrangement of its connections, and the rapidity with which stimuli travel along them.

Test of the Truth of the Hypothesis.—If the hypothesis be true we ought to be able to convert inhibition into stimulation, and *vice versâ*, by either quickening or slowing the transmission of stimuli. We can quicken transmission by heat, and we can render it slower by cold.

On this hypothesis we would expect to find that either excessive quickening or excessive slowing of the passage of stimuli between the cells of the nerve-centres might cause a number of stimuli which would ordinarily interfere to coincide and produce convulsions. This is what actually does occur, for extreme heat and extreme cold both cause convulsions. But it is unsafe to lay too much stress upon this point, as the cause of convulsion may be very complex. We find, however, as we should expect on this hypothesis, that the inhibitory action of the vagus is destroyed by cold.[1]

Explanation of the Actions of Certain Drugs on this Hypothesis.

There are certain phenomena connected with the action of drugs on the spinal cord which are almost inexplicable on the ordinary hypothesis, but which are readily explained on that of interference. Thus belladonna when given to frogs causes gradually increasing weakness of respiration and movement, until at length voluntary and respiratory movements are entirely abolished, and the afferent and efferent nerves are greatly weakened. Later still, both afferent and efferent nerves are completely paralysed, and the only sign of vitality is an occasional and hardly perceptible beat of the heart, and retention of irritability in the striated muscles. The animal appears to be dead, and was believed to be dead, until Fraser made the observation that if allowed to remain in this condition for four or five days, the apparent death passed away and was succeeded by a state of spinal excitement. The fore-arms pass from a state of complete flaccidity to one of rigid tonic contraction. The respiratory movements reappeared; the cardiac action became stronger, and the posterior extremities extended. In this condition a touch upon the skin caused violent tetanus, usually opisthotonic, lasting from two to ten seconds, and succeeded by a series of clonic spasms. A little later still the convulsions change their character and become emprosthotonic. These symptoms are due to the action of the poison upon the spinal cord itself, for they continue independently in the parts connected with each segment of the cord when it has been divided.

[1] Horwath, *Pflüger's Archiv*, 1876, xii. p. 278.

This action may be imitated by a combination of a drug which will paralyse the motor nerves with one which will excite the spinal cord. Fraser concludes that the effects of large doses of atropine just described are due to a combined stimulant action of this substance on the cord, and a paralysing one on the motor nerves. The stimulant action on the cord is masked by the paralysis of the motor nerves, and only appears after the paralysis has passed off. He thinks that the difference in the relations of these effects to each other, which are seen in different species of animals, may be explained by this combination acting on special varieties of organisation. In support of his views he administered to frogs a mixture of strychnine which stimulates the spinal cord, and of methyl-strychnine, which paralyses the motor nerves, and found that the mixture produced symptoms similar to those of atropine. Notwithstanding this apparently convincing proof, it would appear that the paralysis in the frog is due to the action of the atropine on the spinal cord, and not to a paralysing effect on the motor nerves. For Ringer and Murrell have found that when the ends of the motor nerves in one leg are protected from the action of the poison by ligature of the artery there is no difference between it and the unpoisoned leg, while if Fraser's ideas were correct the unpoisoned leg ought to be in a state of violent spasm.

A condition very nearly similar to that caused by atropine is produced by morphine. When this substance is given to a frog, its effects are exactly similar to those produced by the successive removal of the different parts of the nervous system from above downwards. Goltz has shown that when the cerebral lobes are removed from the frog it loses the power of voluntary motion, and sits still; when the optic lobes are removed it will spring when stimulated, but loses the power of directing its movements. When the cerebellum is removed, it loses the power of springing at all; and when the spinal cord is destroyed, reflex action is abolished.

Now these are exactly the effects produced by morphine, the frog poisoned by it first losing voluntary motion, next the power of directing its movements, next the power of springing at all, and lastly, reflex action. But after reflex action is destroyed by morphine, and the frog is apparently dead, a very remarkable condition appears, the general flaccidity passes away, and is succeeded by a stage of excitement, a slight touch causing violent convulsions just as if the animal had been poisoned by strychnine.[1]

The action of morphine here appears to be clearly that of destroying the function of the nerve-centres from above downwards, causing paralysis first of the cerebral lobes, next of the optic

[1] Marshall Hall, *Memoirs on the Nervous System*, p. 7 (London, 1837). Witkowski, *Archiv für exper. Path. und Pharm.*, Band vii. p. 247.

lobes, next of the cerebellum, and next of the cord. But it seems probable that the paralysis of the cord first observed is only apparent and not real; and in order to explain it on the ordinary hypothesis we must assume that during it the inhibitory centres in the cord are intensely excited, so as to prevent any motor action, that afterwards they become completely paralysed, and thus we get convulsions occurring from slight stimuli.

Ammonium bromide also causes, first, complete loss of voluntary movement and reflex action, but at a later stage in the poisoning convulsions.

On the hypothesis of interference, the phenomena produced both by atropine and by morphine can be more simply explained. These drugs, acting on the nervous structures, gradually lessen the functional activity of the nerve-fibrils which connect the nerve-cells together; the impulses are retarded, and thus the length of nervous connection between the cells of the spinal cord, which is calculated to keep them in proper relation in the normal animal just suffices at a certain stage to throw the impulses half a wave-length behind the other, and thus to cause complete inhibition and apparent paralysis.

As the action of the drug goes on, the retardation becomes still greater, and then the impulses are thrown very nearly, but not quite, a whole wave-length behind the other, and thus they coincide for a short time, but gradually again interfere, and therefore we get, on the application of a stimulus, a tonic convulsion followed by several clonic ones, and then by a period of rest. This explanation is further borne out by the fact observed by Fraser, that the convulsions caused by atropine occurred more readily during winter, when the temperature of the laboratory is low, and the cold would tend to aid the action of the drug in retarding the transmission of impulses.[1]

The effect of strychnine in causing tetanus is very remarkable; a very small dose of it administered to a frog first renders the animal most sensitive to reflex impulses, so that slight impressions which would normally have no effect, produce reflex action. As the poisoning proceeds, a slight stimulus no longer produces a reflex action limited to a few muscles, but causes a general convulsion throughout all the body, all the muscles being apparently put equally on the stretch. In man the form assumed by the body is that of a bow, the head and the heels being bent backwards, the hands clenched, and the arms tightly drawn to the body.

My friend Dr. Ferrier has shown that this position is due to the different strengths of the various muscles in the body. All being contracted to their utmost, the stronger overpower the weaker, and thus the powerful extensors of the back and muscles

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[1] *Transactions of the Royal Society of Edinburgh*, vol. xxv. p. 467.

of the thighs keep the body arched backwards and the legs rigid, while the adductors and flexors of the arms and fingers clench the fist and bend the arms, and draw them close to the body.[1] The convulsions are not continuous, but are clonic; a violent convulsion coming on and lasting for a while, and then being succeeded by an interval of rest, to which after a little while another convulsion succeeds. The animal generally dies either of asphyxia during a convulsion, or of stoppage of the heart during the interval.

When the animal is left to itself, the convulsions—at least in frogs—appear to me to follow a certain rhythm, the intervals remaining for some little time of nearly the same extent.

A slight external stimulus, however, applied during the interval—or at least during a certain part of it—will bring on the convulsion. But this is not the case during the whole interval. Immediately after each convulsion has ceased I have observed a period in which stimulation applied to the surface appears to have no effect whatever.

It is rather extraordinary, also, that although touching the surface produces convulsions, irritation of the skin by acid does not do so.[2]

The cause of those convulsions was located in the spinal cord by Magendie in an elaborate series of experiments, which will be described later on (p. 177).

Other observers have tried to discover whether any change in the peripheral nerves also took part in causing convulsion; but from further experiments it appears that the irritability of the sensory nerves is not increased.[3]

According to Rosenthal, strychnine does not affect the rate at which impulses are transmitted in peripheral nerves; he, however, states that it lessens the time required for reflex actions. Wundt came to the conclusion that the reflex time was on the contrary increased.

In trying to explain the phenomenon of strychnine-tetanus on the hypothesis of interference, one would have been inclined by Rosenthal's experiments to say that strychnine quickened the transmission of impulses along those fibres in the spinal cord which connect the different cells together.

The impulses which normally, by travelling further round, fell behind the simple motor ones by half a wave-length, and thus inhibited them, would now fall only a small fraction of a wave-length behind, and we should have stimulation instead of inhibition.

Wundt's conclusion, on the other hand, would lead to the

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[1] *Brain*, vol. iv. p. 313.

[2] Eckhard, Hermann's *Handb. d. Physiol.*, Band ii. Th. 2, p. 43.

[3] Bernstein, quoted by Eckhard, *op. cit.* p. 40. Walton, Ludwig's *Arbeiten*, 1882.

same result by supposing that the inhibitory wave was retarded so as to fall a whole wave-length behind the motor one. On the assumption, however, that the fibres which pass transversely across from sensory to motor cells, and those that pass upwards and downwards in the cord connecting the cells of successive strata in it, are equally affected, we do not get a satisfactory explanation of the rhythmical nature of the convulsions. By supposing, however, that these are not equally affected, but that the resistance in one—let us say that in the transverse fibres—is more increased than in the longitudinal fibres, we shall get the impulses at one time thrown completely upon each other, causing intense convulsion, at another half a wave-length behind, causing complete relaxation, which is exactly what we find.

This view is to some extent borne out by the different effect produced by a constant current upon these convulsions, according as it is passed transversely or longitudinally through the spinal cord. Ranke found that when passed transversely it has no effect, but when passed longitudinally in either direction it completely arrests the strychnine convulsions, and also the normal reflexes which are produced by tactile stimuli.

Ranke's observations have been repeated by others with varying result, and this variation may, I think, be explained by the effect of temperature.

The effect of warmth and cold upon strychnine-tetanus is what we would expect on the hypothesis of interference. With small doses of strychnine, warmth abolishes the convulsions, while cold increases them. When large doses are given, on the contrary, warmth increases the convulsions, and cold abolishes them.[1]

We may explain this result on the hypothesis of interference in the following manner:—

If a small dose of strychnine retard the transmission of nervous impulses so that the inhibitory wave is allowed to fall rather more than half a wave-length, but not a whole wave-length, behind the stimulant wave, we should have a certain amount of stimulation instead of inhibition. Slight warmth, by quickening the transmission of impulses, should counteract this effect, and should remove the effect of the strychnine. Cold, on the other hand, by causing still further retardation, should increase the effect. With a large dose of strychnine, the transmission of the inhibitory wave being still further retarded, the warmth would be sufficient to make the two waves coincide, while the cold would throw back the inhibitory wave a whole wave-length, and thus again abolish the convulsions.

The effect of temperature on the poisonous action of guanidine is also very extraordinary, and is very hard to explain on the

[1] Kunde and Virchow, quoted by Eckhard, *op. cit.* p. 44; Foster, *Journal of Anatomy and Physiology*, November 1873, p. 45.

ordinary hypothesis, although the phenomena seem quite natural when we look at them as cases of interference due to alterations in the rapidity with which the stimuli are transmitted along nervous structures.

Another cause of tetanus that is difficult to understand on the ordinary hypothesis of inhibitory centres is the similar effect of absence of oxygen and excess of oxygen. When an animal is confined in a closed chamber without oxygen, it dies of convulsions; when oxygen is gradually introduced before the convulsions become too marked, it recovers. But when the pressure of oxygen is gradually raised above the normal, the animal again dies of convulsions. This is evidently not the effect of mere increase in atmospheric pressure, but the effect of the oxygen on the animal, inasmuch as twenty-five atmospheres of common air are required to produce the oxygen-convulsions, while three atmospheres of pure oxygen are sufficient. This effect is readily explained on the hypothesis of interference by supposing that the absence of oxygen retards the transmission of impulses in the nerve-centres; so that we get those which ought ordinarily to inhibit one another coinciding and causing convulsions. Increased supply of oxygen gradually quickens the transmission of impulses until the waves first reach the normal relation, and then, the normal rate being exceeded, the impulses once more nearly coincide, and convulsions are produced a second time.[1]

The effect of various agents also in arresting or inhibiting muscular action suggests the possibility that such inhibition is due to interference with vibrations in muscle. The vibrations of the parts which occur in the muscle during the passage of a constant current have already been mentioned. When a constant current is passed for a length of time and then stopped, tetanic contraction of the muscle occurs and lasts for some time, but it can be at once arrested by again passing the constant current through the muscle.

The idea that coincidence or interference of contractile waves in muscle have much to do with the presence or absence of contraction of a muscle has been advanced by Kühne, in order to explain the phenomenon observed by A. Ewald. When the sartorius of a frog is stimulated at each end by electric currents passing transversely through the ends, the secondary contraction which can be obtained from it is strongest in the middle of the muscle, while the points exactly intermediate between the middle and the end do not produce any secondary contraction at all. This absence of secondary contraction Kühne thinks is due to

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[1] For other observations on interference as a cause of inhibition, *vide* Wundt, *Untersuchungen zur Mechanik der Nerven und Nervencentren.* 1876. (Stuttgart: T. Enke); Ranvier, *Leçons d'Anatomie Générale. Année* 1877–78. (Paris: J. B. Baillière et Fils); and Lauder Brunton 'On the Nature of Inhibition and the Action of Drugs upon it' (*Nature*, March 1883, and reprint).

interference, and the powerful secondary contraction from the middle to coincidence of waves.[1]

Inhibition may also be produced by direct irritation of involuntary muscular fibre. Thus I have noticed, under Ludwig's direction, that stimulation of veins as a rule very frequently causes dilatation at the point of irritation, and if the muscular fibre of a frog's heart be injured by pinching at one point, that point is apt to remain dilated when the rest is contracted. Protoplasmic structures appear to be similarly affected, and the passage of an interrupted current through the heart of a snail will arrest its rhythmical pulsations, although the heart in this animal appears to be a continuous protoplasmic structure and destitute of nerves.[2]

Stimulating Action of Drugs on the Reflex Powers of the Cord.

The reflex action of the cord is greatly increased by certain drugs, more especially by ammonia and by strychnine. The action of strychnine was first investigated by Magendie, and his research is not only the first example of the systematic investigation of the physiological action of a drug leading to its therapeutical employment, but is such a model of this method of research that it is worth giving in detail.

He first introduced a little of the upas poison, of which strychnine was the essential ingredient, under the skin of the thigh of a dog, and found that for the first three minutes no symptoms at all were produced. Then the action of the poison began to manifest itself by general malaise, succeeded by marked symptoms. The animal took shelter in a corner of the laboratory; and almost immediately afterwards convulsive contraction of all the muscles of the body occurred, the fore-feet quitting the ground for a moment on account of the sudden extension of the spine. This contraction was only momentary, and almost immediately afterwards ceased; the animal remained calm for several seconds, and was then seized with a second convulsion, more marked and prolonged than the first. These convulsions succeeded each other at short intervals, gradually becoming more severe. The respiration was hurried, the pulse quick, and it was observed that each time the animal was touched a convulsion immediately followed. Finally, death occurred at an interval increasing with the age and strength of the animal.

These symptoms suggested to Magendie the following explanation of the action of the poison.

It was, he thought, absorbed from the wound into the blood,

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[1] *Untersuchungen a. d. Physiolog. Inst.*, Heidelberg, 1879. *Sonderabdruck*, p. 40.

[2] M. Foster, *Pflüger's Archiv.*

by which it was carried to the heart, and thence to all the organs of the body. On arriving at the spinal cord, it acted upon it as a violent excitant, producing the same symptoms as mechanical irritation or the application of electricity. Magendie was not content until he had tested his theory by experiment. The first question to be settled was **whether the poison was absorbed or not.**

To test this supposition he applied the poison first to the serous membranes, the peritoneum and pleura, from which, as he had learned by previous experience, absorption takes place with extreme rapidity. The result showed that his supposition was correct. The symptoms appeared almost immediately after the injection of the poison into the pleura, and within twenty seconds after it had been injected into the peritoneum. In order to ascertain whether absorption took place from mucous as well as from serous surfaces, he isolated a loop of small intestine by means of two ligatures, and injected a little of the poison into the part between them. In six minutes, symptoms of poisoning appeared, showing that absorption had occurred, but they were less intense than when the poison was applied to the serous surface.

Further experiments showed that absorption took place from the large intestine, from the bladder, and from the vagina; but that it was comparatively feeble and slow. When introduced into the stomach along with food, upas invariably caused death; but the symptoms did not appear until half an hour after it had been taken. This delay might have been due either to absorption from the stomach having taken place very slowly or not at all, so that the drug had passed on to the small intestine, and thence been absorbed into the blood. To determine this point, he isolated the stomach by ligatures applied to its cardiac and pyloric orifices, and then injected a little poison into its cavity.

Under such conditions, symptoms of poisoning were only observed after the lapse of an hour. This showed that while absorption from the stomach did occur, it was much slower than from the small intestine.

The second question was, **Does the poison act through the circulation?** If so, reasoned Magendie, the first symptoms of the action of the poison will come on more slowly when it has far to travel to the spinal cord from the point of introduction, and *vice versâ*. On testing this by experiment, he found that when the poison was injected into the jugular vein, tetanus occurred almost instantaneously, and death took place in less than three minutes, for the upas had only to pass through the pulmonary circulation and heart to the arteries of the cord. When injected into the femoral artery (at D, Fig. 66) the distance to be travelled before reaching the cord would be greatly increased, for the poison must first pass through the artery itself,

through the capillaries, and along the vena cava, traversing the whole distance marked D A B in Fig. 66 before it reached the point where it entered the circulation when it was injected into the jugular. Under these conditions the action should be slow, and experiment showed this to be actually the case, for no symptoms appeared until seven minutes after the injection. Although these experiments of Magendie's appear to prove completely that the upas poison acts through the circulation, a number of persons nevertheless considered that the symptoms were produced through the nervous system by means of so-called sympathy. In order to remove their doubts, Magendie narcotised a dog by means of opium, and then divided all the structures of one leg with the exception of the artery and vein. Into this

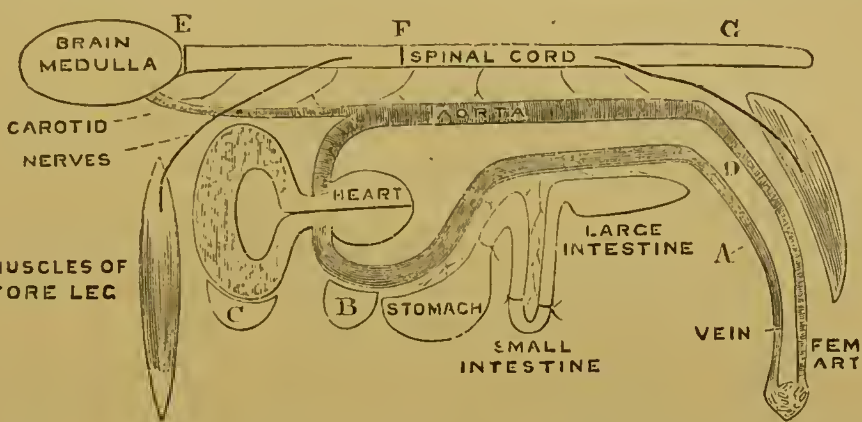


FIG. 66.—Diagram illustrating Magendie's method of investigating the mode of action of upas (strychnine). A, femoral vein; B, peritoneum; C, pleura; D, femoral artery; E, F, G, spinal cord, to which small arteries are seen passing from the aorta. At F is indicated a point of section of the cord.

almost isolated limb he then introduced a little of the poison. This was followed by the usual symptoms almost exactly as if the limb had been intact. By pressing upon the vein which passed from the limb to the body when the symptoms of tetanus appeared he was able to arrest their further development, and by releasing the vessel and allowing the circulation to have free course the symptoms reappeared. Lest by any chance the poison might have acted through nerves or lymphatics contained in the walls of the artery and vein, he divided these structures also, connecting their several ends by means of quills through which circulation then took place. When the poison was applied to the severed limb connected with the body only by these quills, the same succession of phenomena occurred as when the limb was uninjured. The possibility of the action being due to sympathy between the nervous system and the point of application of the poison was thus completely excluded, and the operation of the poison through the circulation triumphantly demonstrated.

The next question was whether the convulsions were caused by the action of the drug on the brain or the cord.

To ascertain its action upon the brain, a little of the solution was injected into the carotid artery. The effects produced were the same as those of any irritating liquid. The intellectual faculties disappeared, the head was laid between the paws, and the animal rolled over and over like a ball. These effects passed off as the circulating blood removed a quantity of the drug from the brain, and were succeeded by the ordinary tetanic convulsions when sufficient time had elapsed for it to reach the spinal cord. The question **whether it really acted upon the cord** still remained to be put to a crucial test. If its effects were really due to its action upon the spinal cord they ought to cease upon the destruction of that part of the nervous system, and to occur when the drug was applied to it alone. The cord was therefore destroyed by running a piece of whalebone down the vertebral canal at the moment of injection. When this was done, no tetanus occurred. In another experiment, Magendie waited until the tetanic spasms had been induced by the upas, and then destroyed the spinal cord by slowly pushing the whalebone down the vertebral canal. As the whalebone advanced, the tetanus disappeared, first in the fore-legs, when the dorsal part of the cord was destroyed, and then in the hind-legs, when the whalebone had reached the lumbar vertebræ.

In another experiment, an animal was narcotised by means of opium, and the spinal canal laid freely open. The upas was then directly placed on a part of the spinal cord. Tetanus immediately occurred in that part of the body, and in that part only to which the nerves arising from this portion of the cord were distributed. When the poison was successively applied to other parts of the cord, the convulsions spread to the corresponding regions of the body.

The question **whether a drug exercises a convulsant action through the brain or spinal cord** is now frequently tested, not by destroying the whole cord as Magendie did, but simply by dividing the spinal cord transversely between the occiput and the atlas. Convulsions depending upon stimulation of the motor centres in the brain and medulla oblongata then cease after section, while those dependent upon the spinal cord do not.

The experiment of dividing the spinal cord transversely about its middle is also sometimes performed in order to test whether the convulsions are of really spinal origin. If they are, they should persist in both the anterior and posterior parts of the body, but if they are of cerebral origin, they occur in the anterior but not in the posterior part.

The effect of strychnine and allied substances upon the cord is usually ascribed to increased excitability of the nerve-cells, but it is not improbably due partly to alteration in the comparative rate at which stimuli are transmitted from one cell to another;

but this subject has already been more fully discussed under 'Inhibition' (*q.v.*, p. 173 *et seq.*).

Some curious results obtained by Dr. A. J. Spence may be explained on the latter hypothesis which would be inexplicable on the former. After removing the blood from the body of a frog, and exposing the brain, he placed some nux vomica upon it, so that it could gradually diffuse along the spinal cord. As it passed downwards he observed that, at first, irritation of the fore-feet caused spasm only in them; later it caused spasm of both front and hind-feet, while irritation of the hind-feet still produced the ordinary reflex; and later still irritation of the fore-feet caused no spasm in the hind-legs while irritation of the hind-feet would still cause spasm in the fore-legs.[1]

The action of strychnine on the conducting power of the spinal cord has already been discussed. It diminishes or abolishes the power of summation, but increases the reflex excitability, so that stimuli will produce reflex action which are too feeble to do so when the spinal cord is in its normal condition. The difference between the reaction to strong and weak stimuli is also to a great extent abolished, and both produce tetanic contractions. This condition, however, is absent for a short time after the application of each stimulus, and then strong and weak stimuli produce corresponding strong and weak action, much as in the normal cord.[2]

The effect of nicotine as a spinal stimulant is very extraordinary; for Freusberg found that when frogs had been decapitated for twenty-four hours, and reflex action was almost entirely gone, the injection of a small quantity of the poison increased the reflex excitability so much that irritation of the skin caused well-marked movements. This increase lasted from one to three days, and the bodies of frogs poisoned by nicotine retained a fresh appearance for a long time.

Spinal Stimulants.

Spinal stimulants are remedies which increase the functional activity of the spinal cord.

Ammonia.	Thebaine.
Strychnine.	Gelsemine.
Brucine.	Buxine.
Absinthe.	Calabarine.
Nicotine.	Caffeine.

The most marked of these are strychnine, brucine, and thebaine, which in small and moderate doses greatly increase the

[1] *Edin. Med. Journ.*, July 1866.
[2] Ludwig and Walton, *Ludwig's Arbeiten*, 1882.

reflex excitability, and in large doses cause tetanic convulsions. Besides these there are some others, such as opium, morphine, and belladonna, which, although they appear at first to have a sedative action, when given in very large doses produce convulsions.

Uses.—The want of an exact knowledge of the intimate pathology of diseases of the spinal cord renders the rational use of spinal stimulants difficult. They are employed in the cases of general debility without any evidence of distinct disease, and in paralysis where there is no evidence of inflammation: this paralysis may be local, or affect the whole side of the body, as in hemiplegia, or the lower half, as in paraplegia.

When strychnine is given in cases of paralysis until it begins to exhibit its physiological action in slight muscular twitches, these twitches begin soooner and are more marked in the paralysed than the healthy parts.

CHAPTER VIII.

ACTION OF DRUGS ON THE BRAIN.

We are able to judge to a certain extent of the order and kind of action of drugs upon the different parts of the nerve-centres by watching their effect upon the movements of animals after their injection.

Functions of the Brain in the Frog.

By removal of successive portions of the nervous system in the frog, Goltz has shown that the **cerebral lobes** have the function of voluntary movement, so that when they are removed, the animal lies quiet, unless acted upon by some external stimulus.

The **optic lobes**, which correspond to the corpora quadrigemina of the higher animals, have the function of directing and co-ordinating movements, but not of originating them, so that a frog in which they are uninjured, but from which the cerebral lobes have been removed, will remain perfectly quiet, except on the application of an external stimulus, when it will leap like a normal frog.

As the optic lobes have the power of directing and co-ordinating movements, when they are destroyed the animal will jump, but will be unable to direct its movements.

The **cerebellum** has also the power of co-ordination, so that when it is removed the animal cannot jump at all, although one leg may answer by a kick or other motion to the application of a stimulus. But even when all those parts have been removed, the frog will still recover its ordinary position after it has been laid upon its back.

The co-ordination requisite for this power of retaining or recovering its ordinary position appears to be situated in the medulla oblongata, for when this is removed the frog will lie upon its back, and will not attempt to recover its ordinary position.

The legs will still respond by movements to irritation applied to the foot, but when the **spinal cord** is now destroyed these reflex movements also cease.

In frogs poisoned by opium, the movements are gradually

abolished in the order just mentioned, and we therefore conclude that opium affects the nerve-centres in the order of their development, the highest being paralysed first, and the lowest last (p. 172). This order is usually not quite the same in higher animals, inasmuch as the last centre to be paralysed by opium or other anæsthetics is usually the medulla oblongata, and more especially that part of it which keeps up the respiratory movements. As we shall afterwards see, however, the respiratory centre is really a lower or more fundamental centre than either the brain or spinal cord.

Functions of the Brain in Mammals.

In higher animals, such as rabbits and guinea-pigs, the cerebral hemispheres are comparatively much more developed than in the frog, and their removal interferes very much with the animal's motions. At first it is utterly prostrate, but after some time its power of movement returns to some extent, though it

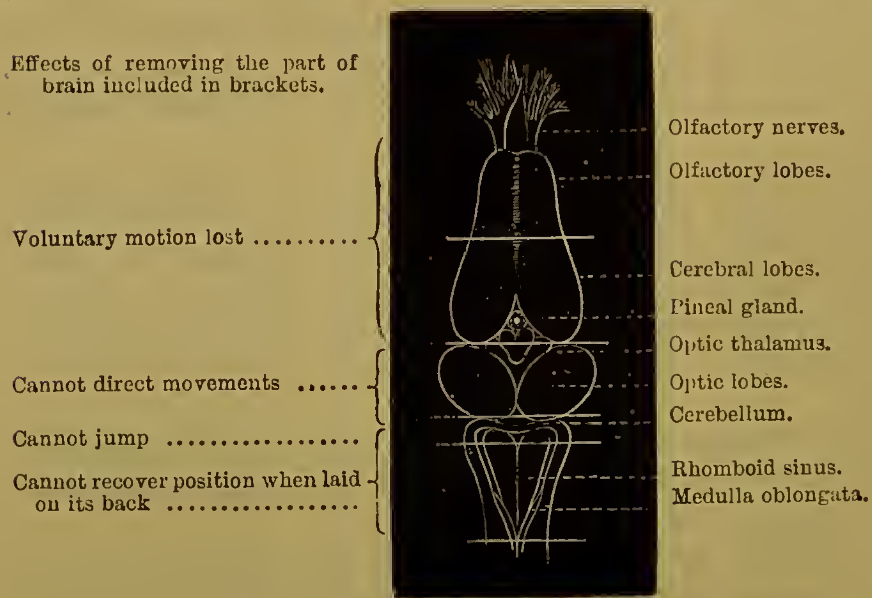


FIG. 67.—Diagram of the higher nerve-centres of the frog.

remains much less than in the normal animal. As we should expect, the weakness is most marked in those parts of the body that are most under the control of the cerebrum, and least in those whose movements are regulated by the lower centres. Thus in rabbits the fore-paws are capable of being used for complex motions at the will of the animal, such as washing the face, holding food, and so on, and in them the weakness caused by removal of the cerebrum is much more marked than in the hind limbs, which are simply used for progression. After the operation the animal can still stand, although it is unsteady, and the fore-legs tend to sprawl out. When pinched it bounds forward, but, unlike the frog, it is unable to avoid any obstacle in its path.

1. The eyes open widely, the pupils dilate, and head and eyes turn towards opposite side.

2. Extension forward of the opposite arm and hand, as if to reach something in front.

3. Movements of tail (and trunk).

4. Retraction with adduction of opposite arm.

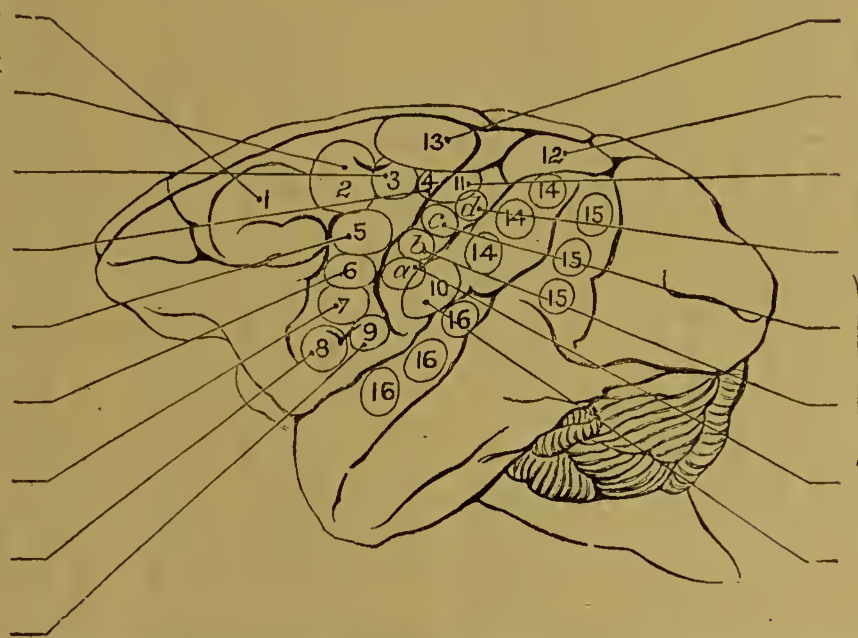
5. Supination and flexion of the fore-arm, by which the arm is raised towards the mouth.

6. Action of zygomatics, by which the angle of mouth is retracted and elevated.

7. Elevation of ala of nose and upper lip.

8. Opening of mouth with protrusion of tongue.

9. Retraction of tongue.



13. Complex movements of thigh, leg, and foot.

12. Advance of the opposite hind limb.

11. Retraction and adduction of opposite arm.

a, *b*, *c*, *d*, Prehensile movements.

10. Retraction of opposite angle of mouth.

FIG. 63.—Brain of monkey, showing the position of the motor and sensory centres as ascertained by Ferrier. The actions all occur on the side of the body opposite to the part of the brain irritated.

If it be pinched at all severely, it not only moves, but will cry loudly and plaintively, and this condition is frequently noticed in rabbits under chloroform, although they have received no injury whatever. The pupils contract on the stimulus of light, and the eyes wink if the finger is brought near them. Bitter substances cause movements of the tongue and mouth, and ammonia applied to the nostrils may cause the head to be drawn back, or the animal to rub its nostrils with its toes.[1]

Where the cerebral hemispheres are still more developed, as in cats, dogs, and monkeys, their removal causes so much prostration, and interferes so greatly with motor power as almost entirely to destroy equilibrium and co-ordinated progression.

The motor and sensory centres of the brain have been more exactly localised in monkeys by Ferrier, Fritsch, Hitzig, and others, and the results of their experiments, especially those of Ferrier, agree so well with those of pathological observation in men that we may assume that there is a general agreement between the position of the centres in man and monkey.

The **motor centres** are arranged along the two sides of the fissure of Rolando, the order of their arrangement being exactly what is required for the purpose of (1) seeing food; (2) conveying it to the mouth; (3) masticating it; (4) throwing away the refuse; and (5) advancing to get more[2] (*vide* Fig. 68, brain of monkey).

The **sensory centres** lie in the posterior and lower parts of the brain. The centre for sight is situated in the angular gyrus and is marked 14 and 15 in the diagram; that for hearing is situated in the superior temporo-sphenoidal and is marked 16 in the diagram; those for smell and taste lie at the tip of the temporo-sphenoidal lobe, and the centre for general sensation appears to be towards the interior of the brain, in the hippocampal region.

When the motor centres in the monkey are slightly irritated by a faradaic current, a single co-ordinated movement is produced, but if the irritation be continued longer, and especially if a strong current be used, epileptiform convulsions may occur, succeeded by choreic movements after the current has ceased. Epileptic convulsions are easily produced by irritation of the cerebral cortex in the cat and dog as well as the monkey. It is difficult to produce them by cortical irritation in the guinea-pig or rabbit, and impossible in birds, frogs, and fishes.[3]

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[1] Ferrier, *Functions of the Brain*, p. 38.

[2] Lauder Brunton 'On the Position of the Motor Centres in the Brain in regard to the Nutritive and Social Functions,' *Brain*, vol. iv. p. 1.

[3] François-Franck and Pitres, *Arch. de Physiol.*, July 1883, p. 39.

Depressant Action of Drugs on the Motor Centres.

The **excitability of the brain** may be altered either by conditions which modify the nerve-cells or the circulation. A deficient circulation greatly depresses the excitability, and it is very low when much hæmorrhage has occurred.

One method of investigating the action of drugs on the excitability of the brain consists in trephining so as to expose the cortical substance and then stimulating it by a faradaic current before and after the administration of a drug either by inhalation or injection. Another method has been employed by Albertoni, who first trephines on one side, and having estimated the strength of current sufficient to produce an epileptic convulsion when applied to a motor centre, he allows the wound to heal, and then gives for a length of time the drug on which he wishes to experiment. He then exposes the corresponding motor area on the other side and observes whether the strength of current required to produce an epileptic convulsion is greater or less than before.

The excitability of the motor centres is greatly lowered by anæsthetics, so that as anæsthesia becomes deeper, irritation of the motor centres has less and less effect, and when anæsthesia is very profound, such irritation has no action whatever.[1] The motor centres, however, are less affected than the sensory ones by anæsthetics, so that they will still react to faradaic irritation when the sensation of pain has been completely abolished.

Alcohol also diminishes the excitability of the motor centres, so that the epileptic convulsions which usually follow the application of strong currents to the cortex are less readily produced after its administration, as well as after ether and chloroform.[2] Chloral for a time diminishes the excitability of the brain, lengthening the latent period, so that stronger currents or more numerous stimuli must be used to produce a result: it will temporarily abolish the excitability. Cold (not freezing) greatly lowers or destroys excitability, and this may be followed by a period of increased excitability with a shorter latent period.[3]

Bromide of potassium, according to Albertoni, when given for several weeks together, greatly diminishes the excitability of the motor centres, so that when dogs are thoroughly under its influence it is almost impossible to produce epileptic convulsions by

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[1] This was observed in the case of ether by Hitzig, *Untersuchungen über das Gehirn*, Berlin, 1874. I have had several opportunities of observing the same thing in regard to chloroform when assisting my friend Dr. Ferrier in experiments on the brain.

[2] François-Franck and Pitres, *op. cit.*

[3] De Varigny, *Recherches expérimentales sur l'excitabilité électrique des circonvolutions cérébrales et sur la période d'excitation latente du cerveau.* Paris, 1884, p. 138.

irritation of the cortical substance. Atropine in small doses increases the excitability of the brain in monkeys, but in large doses paralyses it. It greatly increases the tendency to epileptic convulsions in dogs, so that they can be produced by very much slighter stimuli than usual, and strychnine, absinthe, and cannabin have a similar action in this respect.[1] Physostigmine appears to increase the excitability of motor centres in the brain; for when guinea-pigs have been rendered epileptic by section of a sciatic nerve, the administration of physostigmine greatly increases the number of fits.

Irritant Action of Drugs on Motor Centres in the Brain.

Certain drugs when administered to animals or taken by man produce **convulsions.** The muscular actions which occur in these convulsive movements may be induced by (*a*) irritation of the motor centres in the spinal cord, (*b*) the motor centres in the medulla oblongata and pons Varolii, or (*c*) cerebral cortex. These centres may be irritated directly by the action of the drug upon them, or they may be stimulated indirectly by the drug causing the blood in them to become venous through its action on the respiratory or circulatory organs. Convulsions of this sort, although caused by the administration of a poison, are really asphyxial, and are similar in character to those produced by suffocation.

Convulsions are usually ascertained to be of **spinal** origin by dividing the cord either at the occiput or lower down in its course and finding that they still persist in those parts of the body which derive their innervation from the spinal cord below the point of section. If they cease in parts of the body innervated by the spinal cord alone, but continue in the parts which retain their nervous connection with the brain, they are regarded as of **cerebral** origin (*v.* p. 179).

It has already been mentioned that irritation of the motor areas in the cortex of the brain will produce epileptic convulsions, but it is probable that such cortical irritation acts through lower ganglionic centres and especially through the medulla oblongata and pons Varolii. Epileptic convulsions can be still more readily produced by irritation of this part of the brain than by irritation of the cerebral cortex, and may be induced by a slight lesion of the pons and medulla by a needle. It is to irritation of this part of the brain by venous blood that asphyxial convulsions are due, for they can still be induced by suffocation or by ligature or compression of all the arteries leading to the brain after all the parts of the brain above the pons have been removed, and they cease when the spinal cord is divided just below the medulla, or the medulla itself

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[1] François-Franck and Pitres, *op. cit.*

divided at its lower end. It is evident that, if the spinal cord be paralysed, the convulsions will not occur though the medulla and pons be irritated; and it has been found that, if its blood-supply is stopped at the same time as the circulation in the pons by ligaturing the aorta in place of the cerebral vessels alone, convulsions do not occur. Probably the absence of convulsions in slow asphyxia is due, at least in some degree, to gradual paralysis of the cord by the long-continued circulation of venous blood through it.

The centre for convulsions in the frog appears to be in the medulla oblongata.

Asphyxial convulsions are usually of an opisthotonic character, because, all the muscles being stimulated at once by the action of the venous blood on the motor centres, the stronger overpower the weaker, and the extensor muscles of the back being more powerful than the flexors bend the spine backwards. Asphyxial convulsions only occur in warm-blooded animals and not in frogs, where the respiratory processes are slow, and entire stoppage of the respiration for a length of time does not render the blood sufficiently venous to act as a powerful irritant. If any drug therefore produces convulsions in the higher animals and not in frogs, the probability is that its convulsive action is indirect and the convulsions it produces are asphyxial. If, on the other hand, it produces convulsions in frogs as well as higher animals, its convulsive action is in all probability due to the direct effect of the drug upon the nerve-centres. In order to ascertain this definitely, however, the usual plan is to see (1) whether the convulsions which occur after the drug has been injected disappear when artificial respiration is commenced, and (2) whether these convulsions are prevented by artificial respiration begun before the injection of the drug and kept up during its action. But even this does not entirely show whether the convulsive action of a drug is direct or indirect, for artificial respiration will not prevent asphyxial convulsions if these should depend upon the action of the drug in stopping the heart and thus arresting the circulation. If it is found that the convulsions occur very shortly after the heart stops, the usual plan is to paralyse the vagus in the heart by atropine, and ascertain whether the convulsive action then occurs. If the drug still produces convulsions when respiration is kept up and the heart is not stopped, it is almost certain that its action is direct upon the nerve-centres.

Experiments to ascertain whether convulsions are asphyxial or not may be conveniently made upon fowls, for the venous or arterial condition of the blood is readily ascertained by the colour of the comb. Thus, in fowls killed by cobra poison, the convulsions come on at the moment the comb becomes livid, and when artificial respiration is begun the convulsions disappear as the comb again regains its normal colour. It is evident that the

colour of the comb will indicate the condition of the blood supplying the brain, even though a venous condition of it should be due to stoppage of the heart and not to failure of the circulation.

Camphor has a curious exciting action both upon the brain and upon the medulla. It produces first rapid succession of ideas, great desire to move, hallucinations which are generally agreeable, and a wish to dance and laugh. In animals it has a similar action, causing wild excitement and constant motion, succeeded by clonic epileptiform convulsions, during which death often occurs. Usually, if they survive the convulsions, they recover; but in man the convulsive stage may be succeeded by paralysis, coma, and death, the parts of the nervous system which are first excited being apparently finally paralysed. The action upon frogs is different from that on warm-blooded animals, for in them it produces such rapid paralysis both of the spinal and motor nerves that convulsions do not occur.

Among other drugs having a powerful convulsant action due to irritation either of the cortical centres or of the medulla and pons are picrotoxin (the active principle of *Anamirta cocculus* or *Cocculus indicus*), cicutoxine (the active principle of *Cicuta virosa*), and the active principle of the nearly-allied *Œnanthe crocata*, coriamyrtin (from *Coriaria myrtifolia*), digitaliresin and toxiresin, which are products of the decomposition of the active principles of digitalis.

The **method of localising** the parts of the brain upon which certain drugs exert a **convulsant action**, consists in **extirpating** some of the **motor centres** and then giving these drugs, such as picrotoxin, cinchonidine, and quinine,[1] which produce epileptic convulsions.[2] The results of these experiments are that the epileptic convulsions produced by these poisons appear to have a twofold origin, (*a*) in the brain, and (*b*) in the medulla, the centre in the brain being the most sensitive to the action of the poison. In consequence of this, when the poison is given after the destruction of the motor centres on one side in such quantities as not to cause general convulsions, the weakness of the opposite side, due to the lesions, becomes still more evident, probably from the motor excitability of the sound side being increased. When convulsions are produced they are unsymmetrical. Those of the sound side are much stronger, are generally clonic, and apparently arise from irritation of the cerebral centres. Those of the paralysed side are much weaker, are more tonic, and apparently arise from irritation of the medulla.

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[1] I have seen a case in which an epileptic convulsion appeared to be caused by medicinal doses of quinine.

[2] Rovighi e Santini, *Publicazioni del R. Instit. di stud. superiori in Firenze. Sezione di scienze fisiche natur.* 1882, s. 1.

ACTION OF DRUGS ON THE SENSORY AND PSYCHICAL CENTRES IN THE BRAIN.

The effect of drugs upon the higher mental functions can only be ascertained satisfactorily in man. These functions vary in complexity from simple choice to the highest efforts of genius.

The effect of drugs upon the **time required** for **mental processes** is observed by ascertaining, first, the time required for the performance before and after the administration of a drug, and comparing these two times with one another.

The processes generally investigated are, (*a*) the time required for simple reaction; (*b*) for discrimination; (*c*) for decision. The **simple reaction** is ascertained by marking on a chronograph the time when a signal is made, such as, for example, the exhibition of a coloured flag. As soon as this is seen by the individual experimented upon he marks the time upon the same chronograph by placing a finger upon a key which is connected with the registering electro-magnet. The difference of time between the exhibition of the flag and the time registered by the electro-magnet is equal to the time required for the transmission of the sensory impulse to the brain, for its transmission from the sensory to the motor tracts of the brain, for its passage down the motor nerves, and the latent period of the muscles.

The time required for selection is ascertained in the same way, but either a red or blue flag may be shown, and the person experimented upon has to discriminate between them, and only to press when the one previously agreed upon is shown. The difference between the time of this experiment and the former gives the time required for **discrimination.**

The time required for **decision** is ascertained in the same way as the previous one, excepting that a different signal is to be made on the appearance of the red and of the blue.

Simple reaction has been found by Kraepelin [1] to be little affected by nitrite of amyl: sometimes it is a little quicker and sometimes a little slower than normal. It is rendered slower by ether and much slower by chloroform, although exceptionally it may be quickened by chloroform, probably when used in small doses.

The time required for discrimination is not definitely affected by nitrite of amyl, being sometimes increased and sometimes diminished. It is generally increased, though it may be diminished, by small doses of ether and also by chloroform.

The time for decision is sometimes increased and sometimes diminished by nitrite of amyl. It is increased by ether and also

[1] Kraepelin, *Ueber die Einwirkung einiger medicamentosen Stoffe auf die Dauer einfacher psychischer Vorgänge*, 1882. Abstract in *Rivista Sperimentale di Freniatria*, anno ix. 1883, p. 124.

by chloroform; and if the quantity given be great, the increase may be very large.

The influence of alcohol upon psychical processes is curious; for while it renders them much slower, the individual under its influence believes them to be much quicker than usual.

Drugs which increase the Functional Activity of the Brain.

Nerve Stimulants.

These are remedies which **increase** the **nervous activity** of the cerebro-spinal system. They are subdivided into those which act on the cerebrum, or cerebral stimulants, and those which affect the spinal cord, or spinal stimulants. Spinal stimulants have been already discussed (p. 181).

Cerebral Stimulants.

In popular language, the name of stimulant is generally applied to drugs which have the power to increase the activity of the brain. From their producing a feeling of comfort and mirth they are also called **exhilarants**. The functional activity of the brain, like that of other organs, depends upon the tissue-change which goes on in the cells and fibres which compose it, and the amount of tissue-change is regulated to a great extent by the quantity and quality of the blood supplied to the organ. A free supply of blood to the brain may be obtained by general excitement of the circulation, i.e. more powerful and rapid action of the heart and contraction of the vessels in other parts of the body driving blood into the brain, or by local dilatation of the cerebral arteries allowing blood more ready access to the brain, or by a combination of these factors.

Free circulation through the cerebral arteries may be induced to some extent by **posture**: thus, some men can think best when the head is low, and almost everyone naturally assumes the sitting posture with the head bowed down and held between the hands when suffering from the effects of mental depression. This posture is not, as is often supposed, merely consequent on the depressed condition of the nerve-centres, it is voluntarily assumed because it affords an actual sense of relief. In eager conversation also the body generally stoops forward and the head is held low so as to allow of a free supply of blood to the brain.[1]

This effect of posture on the human brain is admirably shown[2]

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[1] Lauder Brunton on the Physiological Action of Alcohol, *Practitioner*, 1876, vol. xvi. p. 127.

[2] François-Franck et Brissaud, *Marey's Travaux*, 1877, tome iii. p. 147.

by a tracing taken from a patient with an aperture in the skull by François-Franck and Brissaud (Fig. 69).

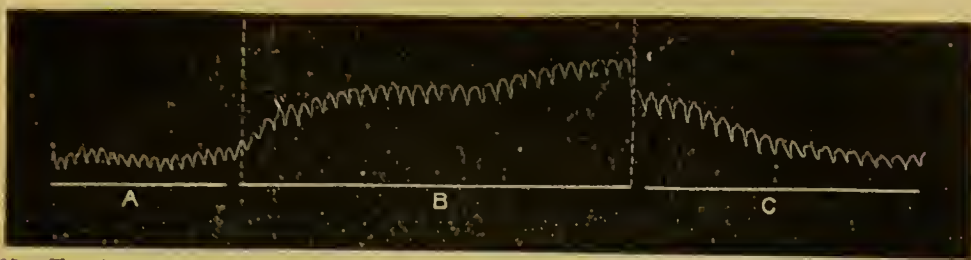

FIG. 69.—Tracing showing the increased circulation in the brain caused by inclining the head and body forwards. The tracing was taken by Brissaud and François-Franck, from the parietal region of a woman who had lost a large piece of bone from syphilis.[1]

Local dilatation of the arteries of the brain appears to be produced in animals by the movements of **mastication** (Fig. 70) and probably also by savoury food or irritating substances in the mouth.

FIG. 70. Tracing to show the increased rapidity of circulation in the carotid of a horse during mastication. (After Marey.)

It is probably on this account that so many substances are **chewed** for their stimulant action, such as tobacco, betel nut, cola nut, and raisins. The effect of smoking is probably to a great extent due also to its action on the cerebral circulation through the stimulating effect of the smoke on the nerves of the mouth and nares, and so is the use of alcohol in sips by men, such as jour-

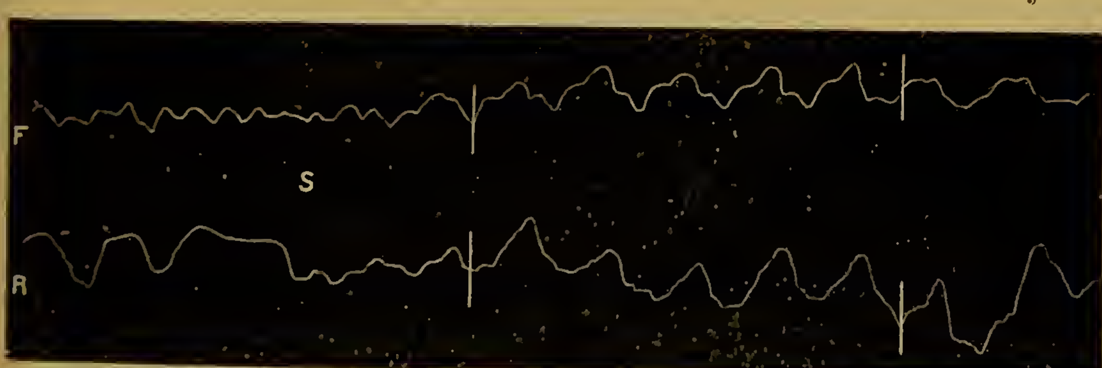

FIG. 71.—Pulsations of the fontanelle (F) in an infant six weeks old while sucking. It shows a simultaneous tracing of the thoracic respiration. The breast was offered to the child at the beginning of the tracing. At the time indicated by the third respiratory wave, which has a flattened top, the child began to take the breast. It will be noticed that the line of the tracing F rises, indicating increased circulation on the brain. (After Salathé.)[2]

nalists, who are engaged in writing. It is probable that tea and coffee also cause local dilatation of the arteries supplying the

[1] *Marey's Travaux* for 1877, p. 147.
[2] Salathé, *Marey's Travaux*, 1876, p. 354.

brain. Suction also causes an increased supply of blood to the brain (Fig. 71).[1]

The effect of local dilatation of the cerebral vessels is very greatly increased, if in addition to it the general circulation is increased and the blood-pressure raised by contraction of the arterioles in the body generally, or by more vigorous action of the heart.

General excitement of the circulation is induced by **exercise** short of fatigue, and a brisk walk will sometimes remove a condition of low spirits. Sometimes the supply of blood to the brain is but slightly increased during continuous exercise, as a large portion of the blood is then diverted to the muscles, but after the exertion is over the excitement of the circulation continues for some time, and then the supply to the brain is increased. In some persons a cold wind acts as an exhilarant, causing contraction of the vessels, with consequent increase in the general blood-pressure and increased circulation in the brain. In persons who are debilitated and feeble, on the contrary, the cold may have an opposite effect, by depressing the action of the heart.

Some men can think best when walking about, on account of the excitement in the circulation which the exertion produces; but many such people, when they come to a very difficult point, will stand still or sit down, so as to allow the blood to flow more to the head and less to the muscles.

Where the circulation is feeble, so that the heart is not much stimulated by walking about, men often find that they can think better when lying down, or sitting with their head in their hands (Fig. 69), so as to gain the advantage of the greater flow of blood to the head in these positions.

Stimulation of the mucous membrane of the nose by smelling the vapour of strong ammonia, carbonate of ammonium, or acetic acid, raises the blood-pressure generally throughout the body by reflexly stimulating the vaso-motor centre, and thus increases the circulation of blood in the brain. Smelling salts or aromatic vinegar are therefore frequently employed, not only to enable people to attend more readily to any subject in which they are engaged, and to prevent them from falling asleep, but also to arouse them from syncope.

The action of **sipping** is a powerful stimulant to the circulation, for, as Kronecker has shown, the inhibitory action of the vagus on the heart is abolished while the sipping continues, and the pulse-rate is very greatly increased. A glass of cold water slowly sipped will produce greater acceleration of the pulse for a time than a glass of wine or spirits taken at a draught. Sipping cold water has been recommended to allay the craving for alcohol in drunkards endeavouring to reform, and probably its use is owing to this stimulant action on the heart. It is sometimes said that a single glass of ale sucked through a straw will intoxi-

[1] Salathé, *op. cit.*

cate a man, although three times the quantity would not do so if taken in large draughts. If this be true, the more rapid intoxication caused by sucking is probably due to the conjoined effects of the alcohol and of temporary paralysis of the vagus caused by the suction, possibly aided by the direct effect of suction on the cerebral circulation (Fig. 71, p. 193).

One of the most typical stimulants is **alcohol.** In small quantities it increases the arterial tension by locally stimulating, first the sensory nerves of the mouth, and afterwards those of the stomach, and thus causing reflex contraction of the vessels and reflex acceleration of the beats of the heart. This effect occurs before its absorption, and is best marked when the alcohol is strong, and is but slightly marked when it is diluted. It is possible that by inducing local dilatation of the cerebral arteries while the heart still continues active, it may have a stimulant action on the cerebral functions, besides that which it induces by merely exciting the circulation generally.

Any stimulant action on the brain beyond what may be explained in this way is very slight, if indeed it exist at all. Its further actions are those of paralysis exerted on the nerve-centres in the order of their development, the higher centres being paralysed first (see p. 146).

At or about this point the stimulating action ceases and the narcotic action commences. The **exhilarating** effect of alcohol, however, may be most marked just at this point, because just here, while the circulation in the brain generally remains increased, the restraining or inhibitory parts of it begin to be paralysed. Thus, imagination and emotion are more readily excited and expression is free and unrestrained; external circumstances are less attended to, and a boyish or childish hilarity occurs.

It is probable that some substances, such as strychnine, increase the mental powers by a direct action on the brain-tissue itself, and possibly caffeine may do so also.

Drugs which lessen the Functional Activity of the Brain.

These drugs are soporifics or hypnotics; narcotics; anodynes or analgesics; and anæsthetics.

Most of the substances belonging to those classes have a certain resemblance to one another in their action. Most of them stimulate the mental functions when given in very small doses. In larger doses they have also a stimulating action at first, i.e. while a small quantity only has been absorbed, but later on they diminish or abolish the mental faculties. The same drug—as, for example, opium or alcohol—in different doses may thus act as a stimulant, narcotic, soporific, and anæsthetic.

In a certain stage of their action opium and alcohol do not

merely lessen the functional activity of the brain, but they **disturb** the normal **relations** of one part to another, so as to produce disorder of the mental functions. Bromide of potassium, on the other hand, appears simply to lessen the functional activity of the brain without disturbing the relation of one part to another. We do not know what the causes of this difference in their action are, but with some degree of probability we may consider that such substances as bromide of potassium, or the normal products of tissue-waste, such as lactic acid, simply diminish the functional activity of the nerve-cells without disturbing the nervous paths by which they communicate with one another, so that we have merely a general and even diminution of the mental faculties, as in natural sleep. Such substances as alcohol, on the other hand, may be supposed not only to diminish the functional activity of the cells, but also to disturb the rate at which the impulses pass from one cell to another, or to alter the direction in which these impulses are sent, so that instead of the mental activity being lessened in degree but natural in kind, as after the administration of bromide of potassium, we have a disturbance of the functions resembling that which we find in delirium or madness.

Hypnotics or Soporifics.

These are remedies which **induce sleep.** Although many of them are also narcotic, yet we may distinguish between hypnotics and narcotics. Pure hypnotics are substances which in the doses necessary to produce sleep do not disturb the normal relationship of the mental faculties to the external world.

In sleep the cerebro-spinal system, with the exception of the medulla oblongata, is to a great extent functionally inactive, and even the respiratory centre and the vaso-motor centre in the medulla, undergo a diminution in their functional activity, so that the respiration becomes slower, the vessels of the surface dilate, and the arterial tension falls.

Certain parts of the nervous system may still remain functionally active, so that, for example, when the nose is tickled with a hair, reflex movements of the face or hand may occur without awakening the sleeper; and certain parts of the brain may also be active so that dreams occur, which may be afterwards remembered as distinctly as real occurrences, or may produce at the time various movements of the body.

But while individual parts may be active, the **whole cerebro-spinal system** is **not active together**, and thus any co-ordination which may occur between either sensations or motions is incomplete; the dreams are incoherent, and the motions do not affect the whole body, as is seen in sleeping dogs, where the legs make a movement of running, but the animal continues to lie on its side. The functional inactivity of the whole or of the greater

part of the cerebro-spinal system is associated with a condition of **anæmia**, and probably depends to a certain extent upon it. At the same time it is probable that sleep depends also on functional inactivity of the cerebral cells due to accumulation of the products of tissue-waste in or around them.

The arteries of the brain during sleep are contracted, the brain is anæmic, and its bulk is small. On awakening, the arteries become dilated, the circulation becomes rapid, and the brain increases in bulk. Where parts of the brain are active, as in dreaming, increased circulation occurs, but probably this is local and not general.

In considering the **circulation** of the brain, however, a marked distinction must be drawn between the condition of the arteries and veins. So long as the blood is in the arteries it is available for the nutrition of the nervous structures; but once it is in the veins it is no longer available, and its accumulation there will tend to impair nutrition, both by the pressure it exerts on the nervous structures, and by its interference with the supply of arterial blood.

In **normal sleep** the arteries and veins are both contracted, and the brain appears anæmic. In the very act of waking the brain may slightly contract, and this has been thought by Mosso, to whom we owe the observation, to show that sleep does not depend upon anæmia of the brain; but this contraction may be due to the removal of venous blood, preparatory to further arterial supply.

Observations on the brain by trephining appear to show that during ordinary sleep, whether it has come on naturally, or has been induced by narcotics, such as a small dose of opium, the brain is anæmic. During functional activity, either of the whole or of its parts, there is arterial dilatation, with a free supply of blood. During **coma** the veins become dilated and the brain congested.[1] This congestion, however, is utterly different from the arterial congestion of functional activity, for in coma the blood, though abundant in quantity, is stagnating in the veins, and useless for the tissues.

In order to produce sleep, then, two things are necessary :—

1st. To lessen the circulation in the brain as much as possible by diverting blood from it or quieting cardiac action.

2nd. To lessen the functional activity of the organ.

Blood may be **diverted** from the brain by dilating the vessels elsewhere. In weak conditions of the body, with feeble vascular tone, this may occur simply from **position**, and such persons become drowsy when standing or walking about, or when sitting. As soon as they lie down, however, the cerebral vessels having little or no tone, the blood floods the brain, and they are unable to sleep. In such persons, sleep may be sometimes obtained by

[1] Hammond, *On Wakefulness*, 1866, p. 20.

raising the head with high pillows. In such cases, also, vascular tonics, such as **digitalis**, by increasing the contractile power of the arteries leading to the brain, may enable them to resist the increased pressure in the recumbent position, and thus prevent the brain being flooded with blood and allow sleep to be obtained.

FIG. 72.—Tracings from the brain of a dog after trephining, showing the influence of position on the cerebral circulation. In the upper tracing the vertical line shows when the head of the dog was lowered, and in the lower tracing when the head was raised. (Salathé.)[1]

The largest vascular area into which the blood may be drawn away from the brain is that of the intestinal canal. When the vessels in the intestine are contracted, it is almost impossible to obtain sleep. Consequently both man and animals, when exposed to cold, which acting through the thin abdominal walls would cause contraction of the intestinal vessels and drive the blood to the brain, instinctively keep the intestines warm by curling themselves up before going to sleep, and thus covering the abdomen with the thick muscles of the thighs.

Warmth to the abdomen by means of a large poultice outside will also tend to produce sleep; or, in place of a poultice, a wet compress, consisting of linen or flannel wrung out of cold water, and covered with oil-silk, and with two thicknesses of dry flannel placed above it, tends greatly to induce sleep and is most useful for this purpose, especially in children.

Warmth to the interior of the stomach has a somewhat similar action, but it differs from warmth to the exterior in this, that it may, to a certain extent, stimulate the heart as well as dilate the abdominal vessels. Stimulation of the heart is of course objectionable, as it tends to maintain the activity of the brain.

On this account the food or drink should be tolerably warm, but not very hot. Warm milk, either alone, or with bread soaked in it, warm gruel, thin corn-flour, or ground rice, sago, or tapioca, warm beef-tea or soup, or a glass of hot wine and water or spirits and water at bed-time, may all act as soporifics by withdrawing the blood from the brain to the stomach. In the sleeplessness of fever a **wet pack**, by restraining the movements and by diverting blood from the brain to the body generally, is often an efficient soporific.

[1] *Marey's Travaux*, 1876, p. 397.

Cold feet also tend to keep up the tension in the vessels and prevent sleep, and therefore they ought to be warmed either by the use of an india-rubber bag filled with hot water, and covered with flannel, or by rubbing them briskly in cold water and drying them thoroughly before going to bed, or by both means combined.

Cardiac excitement may be lessened by sedatives, one of the most useful of which is **cold**. After hours of weary tossing sleep may sometimes be induced by walking about in a night-dress until cool, or by sponging the surface either with cold or hot water.

The **chief hypnotics** or soporifics are—

Opium.	Hypnone.
Morphine.	Bromide of potassium.
Chloral-hydrate.	Bromide of sodium.
Butyl-chloral-hydrate (croton-chloral).	Bromide of calcium.
	Bromide of zinc.
Hyoscyamus.	Monobromo-camphor.
Cannabis.	Hop.
Paraldehyde.	Lettuce.
Urethane.	Lactic acid.

The most powerful **hypnotics** that we possess are undoubtedly opium and morphine, and they seem to act by depressing the functional activity of the brain itself, although along with this depression an anæmic condition of the organ sets in. Besides their action in producing sleep, even in health opium and morphine have the power of lessening pain and thus removing the effect which painful stimuli have in maintaining a wakeful condition. Bromide of potassium and bromide of ammonium in large doses have also a hypnotic action, and even in smaller doses, when they would not of themselves produce sleep, they appear to lessen cerebral excitement, and allow sleep to come on when other conditions are favourable. Chloral probably causes sleep both by acting on the brain itself and by causing dilatation of the vessels generally. It is therefore a useful hypnotic in persons suffering from Bright's disease, in which there is high tension of the vessels and consequently a tendency to sleeplessness.

A **combination** of hypnotics sometimes answers much better than any one singly. Thus morphine or opium alone sometimes simply cause excitement; but when chloral is given, either along with, or after them, the excitement is quieted and sleep occurs.

A combination also of small quantities, such as five or ten minims, of solution of opium or morphine with five grains of chloral and ten to thirty of bromide of potassium, is sometimes more useful than any one of the three used alone.

Indian hemp also is sometimes used to procure sleep, and

lettuce and lactucarium are also said to have a hypnotic action. Lettuce certainly does seem to have such an action, but how much of it depends upon the juice and how much upon the mechanical effect of the indigestible fibres of the lettuce upon the stomach in drawing blood to it, it would be hard to say. Hops are said to be hypnotic, and their combination with lettuce in the form of a supper consisting chiefly of beer and salad has sometimes a very marked soporific action.

Narcotics.

Narcotics are substances which lessen our relationships with the external world. They are closely related, as I have already stated, to stimulants; and alcohol in the various stages of its action affords us a good example of both stimulant and narcotic action. Alcohol at first excites the cerebral circulation and then begins to paralyse various parts of the brain in the inverse order of their development.

But this order differs in different individuals; for in watching the growth of children we find that the order of development of the nerve-centres in them is not always the same: some talking before they can walk, and others walking before they can talk. In all, however, the powers of judgment and self-restraint are among the last to be completely developed.

While the circulation of the brain is still active, the restraining or depressing effect of present external circumstances, and the restraining effect of training, during previous life, which are stored up as it were in the inhibitory centres, are lessened. The fancy is thus allowed free play and a condition of joyousness and volubility like that of a child occurs. The imagination and memory fail next in some, while the emotions become prominent, and to this follows paralysis or paresis of the power of co-ordination. In others the power of co-ordination is impaired before the mental faculties are much affected, the speech becomes thick and the walking becomes staggering and uncertain. At this stage reflex action still persists, but afterwards it is diminished, then abolished, and finally paralysis of the respiratory centre occurs. The effect of other drugs, such as ether and chloroform, is much the same as that of alcohol.

In the case of opium and Indian hemp, however, there is but little excitement of the circulation, and their effects appear to be due more to alterations in the relative functions of the different parts of the brain.

Belladonna, hyoscyamus, stramonium, and their allies, have a curious effect. They produce delirium of an active character, the patient having a constant desire to speak, move about, or be doing something, while at the same time he feels great languor. It is probable that this effect is due to the combined stimulant

action of these drugs on the nerve-centres in the brain and spinal cord and their paralysing action on the peripheral ends of motor nerves.

Anodynes or Analgesics.

Anodynes are remedies which **relieve pain** by lessening the excitability of nerves or of nerve-centres. They are divided into local or general:—

Local Anodynes.	General Anodynes.
Cold—	Anæsthetics in small doses.
Cold water.	Atropine.
Ice-bags.	Belladonna.
Warmth—	Butyl-chloral.
Poultices.	Chloral.
Fomentations.	Conium.
Aconite.	Coniïne.
Acupuncture.	Gelsemium.
Atropine.	Hyoscyamus.
Belladonna.	Hyoscyamine.
Blood-letting—	Lupulus.
Leeches.	Lupulin.
Cupping.	Morphine.
Carbolic acid.	Opium.
Carbonic acid.	Stramonium.
Cocaine.	
Conium.	
Creasote.	
Gelsemium.	
Hydrocyanic acid.	
Morphine.	
Opium.	
Veratrine.	

Action.—The sensation of pain is due to a change in some part of the cerebrum, and is usually excited by injury to some part of the body.

According to Ferrier the hippocampal region is the seat of sensation. Pain may be of **central** origin; for if these convolutions should from any cause undergo changes similar to what usually take place in them on the application of a painful stimulus to a nerve, pain will be felt, even although no injury whatever has been done to the body. Something of this sort appears to occur in certain cases of hysteria.

Conversely, if the changes which ordinarily occur in these convolutions on severe irritation of a sensory nerve are prevented from taking place, pain will not be felt, however great the stimulus to the nerve may be.

The sensory nerves of the head pass directly to the brain, but

all other sensory nerves have to pass for a greater or less distance along the spinal cord before they reach the brain.

The transmission of painful impressions along the spinal cord occurs in the grey matter, and the effect of anæsthetics in preventing the transmission of painful impressions while tactile stimuli are still conducted has been already discussed.

Pain may be occasioned by irritation applied to nerves anywhere between the brain and the periphery; and whatever its point of application may be, it is usually referred to the **peripheral** distribution of the nerve. Sometimes irritation of a nerve, instead of being referred by the brain to the proper spot, is referred to a branch of the same nerve going to a different point.

Pain may be **caused** by violent stimulation of the peripheral distribution of a nerve, of its trunk, of the spinal cord through which the fibres pass to the brain, or of the encephalic centres themselves.

Pain may be **relieved** by (*a*) removing the source of irritation, (*b*) by preventing the irritation from affecting the cerebrum. Thus, if necrosis of the jaw should give rise to intense pain, the pain will at once cease on dividing the sensory nerve by which the impulses are transmitted to the brain. It may be relieved, also, while the source of irritation still remains, by lessening the excitability of the peripheral terminations of the sensory nerves which receive the painful impression; or of the nerve-trunks; or of the spinal cord along which the impression travels; or of the cerebral centres in which it is perceived.

Opium probably acts on them all, diminishing the excitability of the cerebral centre, of the spinal cord, and of the sensory nerves; and bromide of potassium is also supposed to affect all these structures, though to a much less degree than opium.

Chloral, butyl-chloral, lupulin, gelsemium, and cannabis indica probably act on the **cerebral centres.**

Belladonna and atropine lessen the excitability of the sensory nerves, and probably this is effected also by hyoscyamus, stramonium, aconite, aconitine, and veratrine.

Uses.—It is evident that if the nerve-centre by which pain is perceived is deadened, the pain will cease wherever its seat may be; and therefore opium and morphine are used to relieve pain whatever may be its cause. Cannabis indica and bromide of potassium, having likewise a central action, may also be employed, but they are very much less efficient than opium. Chloral and butyl-chloral have an anæsthetic action when given in very large doses, but in moderate doses their power to relieve pain is not so marked as their hypnotic action. Butyl-chloral, however, seems to have a special sedative action on the fifth nerve, and so has gelsemium: consequently both of them are used in the treatment of facial neuralgia.

As cocaine, belladonna, aconite, and veratrine have a **local** action on the peripheral ends of the sensory nerves, they are usually applied directly to the painful part in the form of lotion, ointment, liniment, or plaster. Local injections of cocaine, morphine, atropine, or ether, in the neighbourhood of the painful part, are often of the greatest service.

Adjuncts to Anodynes.—As pain depends on the condition of the cerebral centre by which it is perceived, as well as on irritation of sensory nerves, it is obvious that it may vary with the condition of these centres, although the irritation remains. Thus a decayed tooth does not always cause toothache, and when the toothache comes on, it may frequently be removed by means of a brisk **purgative**, even although the tooth be not extracted. It is possible that the purgative may act partly by lessening congestion around the tooth, but partly also by altering the condition of the cerebral centres. When the **attention** is fixed upon other things, also, the pain may be to a great extent, or even completely, abolished, as in mesmerism or hypnotism. The sensory stimuli, also, which would usually produce pain may be diverted voluntarily or involuntarily into motor channels. Thus, during the heat of action, the pain of a wound is not felt; and the pain felt during the extraction of a tooth is lessened by the employment of violent muscular effort, as in grasping the arms of the dentist's chair. Other most powerful adjuncts are **electricity** applied along the course of the nerves, and **counter-irritation**, especially by means of the actual cautery to the painful part, and, when other means fail, stretching the nerve may succeed.

Cold also, applied to the surface over a painful part, will relieve pain, and so may dry **heat**, applied by a sand-bag or hot cloth, or moist heat in the form of a poultice; for the mode of action of these *vide* 'ACTION OF IRRITANTS.'

Pain has been ascribed by Mortimer Granville to **vibrations** of **nerves** or of the sheaths; and, in order to lessen it, he proposes to produce vibrations of a different nature: this he does by percussing over the painful nerve with a small hammer, worked either by clockwork or electricity. For a dull heavy pain he uses quick and short vibrations of the hammer, and for a sharp lancinating pain he uses large and slow vibrations.

Anæsthetics.

Anæsthetics are remedies which **destroy sensation.**

It has already been mentioned that both sensation and pain require for their perception a certain condition of the cerebral centres and of the sensory nerves and spinal cord, by which impressions are conveyed to these centres.

The difference between anæsthetics and anodynes is to a great extent one of degree. Anodynes affect more particularly the

cerebral centres by which pain is perceived, or the conducting paths by which painful impressions are transmitted, and thus in moderate doses lessen pain without destroying reflex action. They only affect the ordinary centres for reflex action when the dose is considerably increased. Anæsthetics, on the other hand, affect the cerebral and spinal centres more equally, and so abolish pain, ordinary sensation, and reflex excitability more nearly at the same time, though their abolition is by no means completely simultaneous.

According to Eulenberg, in chloroform-narcosis the patellar reflex is abolished first, then reflex from the skin, then from the conjunctiva, and lastly from the nose. As the anæsthesia passes off they return in the inverse order, patellar reflex being the last to reappear. A stage of excitement generally precedes the disappearance of patellar reflex, both in man and animals.

Narcosis by ether differs from that of chloroform in the much greater increase of patellar and other tendon reflexes, both in extent and duration.

Chloral hydrate and potassium bromide have an action like chloroform, but much weaker. Like chloroform, they paralyse the patellar reflex before the corneal reflex, but butyl-chloral (croton-chloral) paralyses the corneal reflex before the patellar.

In ordinary sleep, reflexes disappear in the same order as in chloroform narcosis, but in mesmeric sleep the reflexes are increased as in narcosis from ether. In hysterical conditions diminution of the cerebral reflexes from the nose and cornea with persistence of the patellar reflex has been observed.

The reflex power of the vaso-motor centre is very quickly paralysed by chloroform, so that irritation of a sensory nerve will no longer raise the blood-pressure. Its reflex power is much less affected by ether.[1]

Anæsthetics may be divided into local and general. The **local** are those which abolish the sensibility of the peripheral nerves of a particular area. The **general** are those which act on the central nervous system in the way already described, and abolish sensation throughout the whole body.

The chief **local anæsthetics** are cold, cocaine, carbolic acid, iodoform.

For the purpose of producing local anæsthesia, cold is generally applied by means of ether spray, until the part is all but frozen and is insensible, when slight operations may be made without the patient feeling any pain. The ether may perhaps have itself a certain amount of physiological effect in diminishing sensibility when applied in this manner. Carbolic acid painted over the surface also causes it to become white and to lose its sensibility, and may thus be used to lessen the pain of opening an abscess.

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[1] H. P. Bowditch and C. S. Minot, *Boston Med. and Surg. Journ.*, May 21, 1874.

General anæsthetics are—

Nitrous oxide.	Trichlorhydrin.
Ether.	Bi-chloride of methylene.
Chloroform.	Paraldehyde.
Bromoform.	Bi-chloride of ethidene.
Tetrachloride of carbon.	Bromide of ethyl.

With the exception of nitrous oxide they all belong to the class of alcohols and ethers, and the substitution-compounds having an anæsthetic action are probably almost indefinite in number. Even alcohol itself produces general anæsthesia when volatilised and inhaled.

General Anæsthetics may destroy the sensibility of the nerve-centres indirectly or directly. Anæsthesia is induced indirectly by **stopping** the **circulation** in the brain and thus arresting the process of oxidation and tissue-change in the nerve-cells which are necessary for their functional activity.

This result may be produced by draining the blood from the head into other parts of the body. Thus in some of the hospitals at Paris, before anæsthetics were introduced, a plan was sometimes employed of rendering a patient insensible before an operation, by laying him flat on the ground, and then lifting him very suddenly to a standing posture by the united efforts of six or eight men (*cf.* pp. 193, 198).

Local arrest of the circulation to the brain by ligatures or by compression of the arteries has a similar effect. Waller has recommended diminution of the cerebral circulation, by the combined effects of simultaneous pressure on the carotid arteries and vagus nerves, as an easy means of producing anæsthesia for short operations.

Slight anæsthesia, usually accompanied by some giddiness, may be produced by taking a number of deep breaths in rapid succession. This may be used in order to lessen the irritability of the pharynx in laryngoscopic examinations, and to lessen the pain of opening boils or abscesses. The anæsthesia thus produced may perhaps depend on anæmia of the brain, although this is not certain.

Anæsthesia may also be produced by **diminishing** the **internal respiration** of the nerve-cells through a gradually increasing venous condition of the blood. Thus gradual suffocation by charcoal fumes or carbon monoxide causes complete insensibility, and the inhalation of nitrogen and of nitrous oxide has a similar action.

Anæsthesia may be caused by the direct action of **drugs** on the **nerve-cells** themselves. Chloroform, ether, and other allied substances belonging to the alcohol series appear to act in this way. Although their action is generally exerted through the blood by which they are conveyed to the brain when inhaled, yet

they will also produce a similar action if locally applied to the nerve-centres. Thus Prevost[1] found that chloroform applied directly to the brain of a frog narcotises it when the aorta is tied. When the aorta is again unligatured, so that the current of blood can again wash the chloroform away, the narcosis disappears. Chloroform and ether when inhaled appear to act like alcohol, producing paralysis of the nerve-centres, commencing with the highest and proceeding downwards. The rate of paralysis, though the same in order, is more rapid than that caused by alcohol.

These anæsthetics are, however, not nerve-poisons only; they are **protoplasmic poisons** affecting simple organisms, such as amœbæ and leucocytes, and destroying also the irritability of muscular fibre.

This action of anæsthetics and especially that of chloroform upon muscular fibre is one of considerable importance in reference to the occasional stoppage of the heart and consequent death during the administration of anæsthetics.

The **action** of **anæsthetics** may be divided into **four stages**:—

1st. The stimulant stage.
2nd. The narcotic and anodyne stage.
3rd. Anæsthetic stage.
4th. Paralytic stage.

Stimulant Stage.—Chloroform and ether, as already mentioned, resemble alcohol in their action, and, like it, in small doses will produce a condition of stimulation and acceleration of the circulation passing gradually into one of narcosis, in which the action of the higher nervous centres is more or less abolished, while that of the lower centres still remains.

In small quantities chloroform and ether are sometimes taken, either internally or by inhalation, for their stimulant effect. They are useful in lessening pain and spasm, as in neuralgia, and biliary, renal, or intestinal colic, when given till the stimulant is just passing into the narcotic stage.

Narcotic Stage.—When pushed still further, sensibility becomes more impaired, reflex action still continues, and sometimes, just as in drunkenness, there is a form of wild delirium and great excitement. This is much less marked in feeble or debilitated persons than in strong men. In the latter, the struggles which occur in this condition are sometimes exceedingly violent, the patient raising himself forcibly from the couch, his muscles being in a state of violent contraction, the face livid, the veins turgid, and eyeballs protruding. Usually this condition quickly subsides and passes into the third stage—that of complete anæsthesia.

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[1] Prevost, *Practitioner* July 1881.

In order to lessen the pains of labour, anæsthesia is usually carried to the commencement of the second stage.

Anæsthetic Stage.—The third stage differs from the second in the function of the spinal cord being abolished, as well as those of the brain; ordinary reflex is consequently abolished, and the most common way of ascertaining whether this stage has set in or not is by drawing up the eyelid and touching the conjunctiva. If no reflex contraction of the eyelid occurs, the anæsthesia is complete. By careful and judicious administration of the anæsthetic this condition may be kept up for a length of time even for hours, or days; but if the inhalation be carried too far, the anæsthetic passes into the fourth stage.

The third stage is the one employed for surgical operations.

Paralytic Stage. — In the fourth the respiratory centre becomes paralysed, respiration ceases, and the beats of the heart become feebler and may cease altogether.

Uses of Anæsthetics.

Anæsthetics are used not only to lessen pain but to relax muscular action and spasm. They are chiefly employed to lessen pain in surgical operations, in labour, and in biliary and renal colic. They are used to lessen muscular action and spasm in tetanus, in poisoning by strychnine, in hydrophobia, and in the reduction of dislocations, fractures, and hernia. They are also of assistance in diagnosis, by allowing careful examination to be made of parts which are too tender or painful to be examined without it, and by causing the phantom tumours due to spasmodic contraction of the muscles to disappear.

Dangers of Anæsthetics.—(1) One danger is that just mentioned, of **paralysis** of the **respiration** from an overdose. This, however, is one of the least of the dangers, and if the enfeeblement of the respiration be observed in time, it is generally possible to save the patient by stopping inhalation, and keeping up artificial respiration for a little while if necessary.

(2) Another danger is from **paralysis** of the **heart** by a too concentrated chloroform vapour. This is indicated by a sudden stoppage of the heart, paleness of the face, and dilatation of the pupil while the respiration may continue.

If this accident should occur, the body of the patient should be inclined so that the head should be lower than the feet, and artificial respiration should be kept up briskly but regularly, the expiratory movements being made by pressure on the thorax and especially over the cardiac region, so that the mechanical pressure should stimulate the heart, if possible, to renewed action. The vapour of nitrite of amyl may also be administered by holding a piece of blotting-paper or cloth on which a few drops have been sprinkled before the nose, while artificial respiration is kept up.

The inspiratory movements may be made by drawing the arms backwards over the head, as in Sylvester's plan.

(3) A third danger arises from stoppage of the heart by a combination of chloroform-narcosis and **shock**. This is one of the most dangerous conditions. It may occur even during full chloroform-narcosis in animals from operations on the stomach; but it is much more common in men from **imperfect anæsthesia.** In very many cases of so-called death from chloroform during operations, we find it noted as a matter of surprise that death should have occurred as the quantity of chloroform given was so small. The reason that death occurred probably was because the quantity of chloroform given was so small. Had the patient been completely anæsthetised, the risk would have been very much less. The reason why imperfect anæsthesia is so dangerous is, that chloroform **does not paralyse all** the reflexes **at the same time.** A very large proportion of the deaths from chloroform occur during the extraction of teeth, and we may take this operation as a typical one in regard to the mode of action, both of the sensory irritation and of the chloroform. When a tooth is extracted in a waking person, the irritation of the sensory nerve produced by the operation has two effects:—1st, it may, acting reflexly through the vagus, cause stoppage of the heart and a consequent tendency to syncope. 2nd, it causes reflex contraction of the arterioles, which tends to raise the blood-pressure and counteract any tendency to syncope which the action of the vagus might have produced.

In complete anæsthesia all these reflexes are paralysed, and thus irritation of the sensory nerves by the extraction of the teeth has **no effect** either upon the vagus or upon the arterioles. In imperfect anæsthesia, however, the reflex centre for the arterioles may be paralysed (*vide* p. 204), while the vagus centre is still unaffected. The irritation caused by the extraction of the tooth may then cause stoppage of the heart, and there being nothing to counteract the tendency to faint, syncope occurs and may prove fatal.

With nitrous oxide there is very much less danger, inasmuch as the nitrous oxide causes a venous condition of the blood, with consequent contraction of the arterioles and rise in the blood-pressure, so that any tendency to syncope through vagus-irritation is efficiently counteracted.

With ether, also, the danger is very much less, probably because it has a more equal effect on the centres (*vide* p. 204).

(4) Another danger is that of **suffocation** from blood passing into the trachea in operations about the mouth or nose, or from the contents of the stomach being drawn into the larynx when vomiting has occurred during partial anæsthesia. In consequence of this, it is better, instead of giving chloroform or ether during the whole of an operation on the mouth or nose, to give it

only at the commencement, and to administer along with it, or before it, a hypodermic injection of one-sixth to one-third of a grain of **morphine.** The chloroform anæsthesia thus passes into the morphine narcosis, and the operation can be finished without pain, and without danger.

To **prevent** the occurrence of **vomiting**, it is advisable not to give solid food for some hours before an operation, though if necessary a little beef-tea or stimulant may be given half an hour or so before the administration of the anæsthetic.

Mode of administering Anæsthetics.—In order to obtain the **first stages** of the action of anæsthetics, as in cases of intestinal, biliary, or renal colic, intense neuralgia, or in parturition, the best means of administration is one for the account of which I am indebted to Mr. W. J. Image, of Bury St. Edmunds. It consists of a tumbler, at the bottom of which is placed a piece of blotting-paper or linen thoroughly wetted with chloroform or ether. The patient holds the tumbler to the nose with his, or her, own hand. On account of the form of the tumbler, sufficient air always gets in at the sides, and the patient cannot inhale the vapour in too concentrated a condition. As soon as the anæsthetic begins to take effect, the hand drops, and the inhalation ceases. As the effect again passes off, the patient resumes the inhalation. In employing anæsthetics in this way, however, great care must be taken that the **bottle** containing the chloroform is never entrusted to the patient, but is always kept on a table at some little distance from the bed, and that the blotting-paper or lint in the tumbler is supplied with fresh chloroform by an attendant. If the bottle itself be entrusted to the patient, as the anæsthetic takes effect and produces stupidity, the stopper may fall out, the whole contents of the bottle may be sucked up by the pillow, bolster, bed, or bedclothes, and the vapour being inhaled, fatal suffocation may ensue.

Another method of administering chloroform, which is very convenient when complete anæsthesia is required for a length of time, and when the supply of chloroform is limited, was devised by Sir James Simpson: it consists of either a cup-shaped inhaler, formed of a wire framework covered with flannel, or else simply of a single fold of a pocket-handkerchief thrown over the face: the chloroform is dropped upon the flannel or handkerchief just under the nostrils in single drops at a time. Another plan is to pour some chloroform on to a folded towel or pocket-handkerchief, and then place it over the patient's face, taking care that it does not come so close over the nose as to interfere with a free admixture of air with the chloroform vapour. There is this difference between ether and chloroform, that whereas it is highly inadvisable to give chloroform vapour in a concentrated condition, it is requisite to give the ether vapour very strong, in order to produce an anæsthetic effect. A combined administration of

nitrous oxide and ether is now used to a considerable extent: the nitrous oxide producing rapid anæsthesia, which is kept up by the ether.

Anæsthesia in Animals.

In the course of many investigations into the action of drugs on animals it is necessary to perform experiments which would be painful unless the animals were anæsthetised. The easiest way of doing this with frogs or small animals, such as mice, rats, or rabbits, is to put them under a bell-jar with an opening at the top. Into this opening a piece of cotton-wool or blotting-paper is put, and chloroform dropped on it. The vapour being heavier than air falls to the bottom, and the animal soon becomes insensible. The best way of anæsthetising cats, small dogs, or very large rabbits, is to put them into a wooden box or tin pail, and stretch a towel tightly over the top. An assistant then pours some chloroform on the towel and anæsthesia is quickly produced. Rats are most readily anæsthetised by completely covering the cage, in which they are, with a towel, and dropping chloroform upon it.

Rabbits may be very quickly anæsthetised by the plan employed by Pasteur. It consists in putting a piece of cloth or blotting-paper soaked in chloroform round the animal's nose so as to exclude air. At once the rabbit ceases to breathe, and remains without breathing for about a minute. It then begins to struggle, and if the anæsthetic be kept closely applied the respiratory movements shortly become steady and regular and the animal completely insensible.

For very large or savage dogs an old packing-case without a lid may be simply placed over the animal and held firmly down, or one of the sides may be furnished with hinges so as to convert the case into a sort of kennel. After the dog is safely housed large pieces of blotting-paper or of cloth on which chloroform is poured are pushed through cracks in the top of the case or holes specially made for the purpose. The outer ends of the blotting-paper or cloth remaining outside, fresh quantities of chloroform can be introduced as required until complete anæsthesia is produced. Anæsthesia may be maintained for almost any length of time that is required, by putting a piece of cloth loosely round the animal's nose and dropping chloroform upon it. This requires careful attention, however, in order to prevent danger from an overdose on the one hand, or partial recovery on the other. I find the most convenient way of maintaining the anæsthesia induced by chloroform in the way already mentioned is to put a cannula in the trachea and connect it with a flask containing ether, so that the inspired air passes over the surface of the ether, and carries a quantity of the vapour with it into the lungs of the

animal. By means of a peculiar stopcock, the construction of which is indicated in the diagram (Fig. 73), pure air or air loaded with ether vapour or a mixture of both may be given.

The advantages of employing this method and of using ether rather than chloroform are that complete anæsthesia may be kept

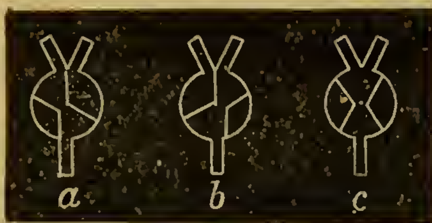

FIG. 73.—Diagram of a stopcock by which air or vapour, or two kinds of gas, may be given alone, or mixed together in any proportion.

up for hours together with little or no attention on the part of the operator, and without the respiration or blood-pressure being seriously affected by the anæsthetic.

Another plan of maintaining anæsthesia for a length of time is to inject some laudanum or liquid extract of opium into a vein after anæsthesia has been induced by chloroform. Before the effect of the chloroform has passed off, such complete narcosis is produced by the opium that no procedure, however painful it might otherwise be, will produce the slightest evidence of sensation. When the effect of the anæsthetic or of the opium would interfere with the investigation of the action of a drug on the circulation or reflex action, the animal may be anæsthetised by chloroform, and the crura cerebri divided. The channels by which painful impressions are conveyed to the brain being thus destroyed no pain can be felt, although the reflex action of the cord again returns after the effects of the chloroform have passed off.

History of the Discovery of Anæsthesia.

This is a subject of considerable interest, and has given rise to much discussion. The starting-point of the discovery seems to have been Sir Humphry Davy's observations on the properties of nitrous oxide, regarding which he said, 'as nitrous oxide in its extensive operation seems capable of destroying physical pain, it may probably be used with advantage during surgical operations.' The property of this gas and also of ether vapour to produce excitement when inhaled, caused these substances to be used in sport, and during their action bruises were frequently received, but not felt. This circumstance excited the attention of Dr. Crawford W. Long, of Athens, Georgia, and, in 1842, he anæsthetised a patient with ether in order to remove a tumour. He was encouraged to do this by the fact that Dr. Wilhite, in a frolic, had rendered a negro boy completely insensible without any bad results. Mr. Horace Wells, without

knowing what Dr. Long had done, used nitrous oxide as an anæsthetic in 1844. His pupil, Mr. Morton, wishing to use it also, asked him how to make it, and was referred to a scientific chemist, Dr. Jackson. Jackson advised Morton to use sulphuric ether, as it had similar properties to nitrous oxide and was easier to get. Acting on this suggestion Morton used ether in dentistry, and induced Drs. Warren, Haywood, and Bigelow to perform important surgical operations on patients whom he anæsthetised by it. From this time onwards anæsthesia has been regularly used in medical operations. Shortly afterwards, Sir J. Y. Simpson discovered the use of chloroform as an anæsthetic, and it has been chiefly employed in Great Britain, but in America ether has always retained its original place.

Antispasmodics.

These are remedies which **prevent** or **relieve spasm.**

Spasm is contraction of voluntary or involuntary muscles, in a way that is unnecessary or injurious to the organism generally. The spasmodic contraction of muscles may sometimes be excessive in degree, as in the calves of the legs in cramp, or in the fibres of the intestinal walls in colic. Sometimes it is not excessive in degree, but are merely out of place, as, for example, in the slight twitchings of the face or fingers which occur in mild cases of chorea.

Spasm may affect single muscles, or it may affect groups of muscles and the nerve-centres by which they are set in action; these centres may sometimes be very limited in extent, but sometimes a great number, or indeed most of the motor centres in the body, may be involved, as in the convulsions of hysteria. Spasm is, indeed, a kind of insubordination in which the individual muscles or nerve-centres act for themselves without reference to those higher centres which ought to co-ordinate their action for the general good of the organism. It may be due, therefore, either to excess of action in the muscles or local centres, or diminished power of the higher co-ordinating centres. As a rule it is due to diminished action of the co-ordinating or inhibitory centres, rather than to excess of action in the motor centres; it is, therefore, a disease rather of **debility** and deficient co-ordination than of excessive strength.

Cramps in the muscles may come on from their exhaustion by excessive exertion, the waste products of their functional activity appearing to act as local irritants. This is relieved by the removal of these waste products; as, for example, by shampooing. In the intestine, cramp may be due to the presence of a local irritant, which ought in the normal condition to produce increased peristalsis, and thus ensure the speedy removal of the offending substance. From some abnormal condition the muscular fibres

around the irritant contract excessively, and do not pass on the stimulus to those adjoining. From this want of co-ordination painful and useless spasm occurs. In order to remove it we apply **warmth** to the abdomen so as to increase the functional activity, both of the muscular fibres and of the ganglia of the intestine (pp. 138, 140). Peristalsis then occurring instead of cramp, the pain disappears, and the offending body is passed onwards and removed. Or we give internally aromatic oils, which will have a tendency to increase the regular peristalsis; or yet again, we may give opium for the purpose of lessening the sensibility of the irritated part, or the nerves connected with it, and thus again bringing it into relationship with other parts of the body.

General antispasmodics may **act** either

(1) By increasing the power of the higher nervous centres to keep the lower ones and the muscles in proper subordination, or—

(2) By lessening the activity of over-excited muscles or lower nervous centres.

On this account we find stimulants and antispasmodics very much classed together. Those drugs which **stimulate** the circulation and increase the nutrition of the higher nerve-centres and the **co-ordinating power,** tend to prevent spasm. Thus, small quantities of alcohol and ether, by acting in this way, tend to prevent general spasm, as in hysteria, nervous agitation, or trembling, or remove local spasm, as in colic.

Camphor, which is frequently used as an antispasmodic, has a stimulant action on the brain, spinal cord, circulation, and respiration. It is probable that such antispasmodic powers as it possesses are due to its exciting the higher centres, and increasing their inhibitory powers over the lower (p. 214). Bromo-camphor has a somewhat similar action.

Valerian, asafœtida, musk, castor, and other aromatic substances, have an antispasmodic action which we do not understand. It is possible that they affect some part of the brain particularly, so as to increase its regulating power, in much the same way as camphor.

Other antispasmodics, such as bromide of potassium, **lessen** the **irritability** of motor centres. Borneol and menthol have a depressing and finally paralysing effect upon motor, sensory, and reflex centres in the brain and spinal cord. In this respect they differ greatly from ordinary camphor, which has an exciting action upon these structures, though they may perhaps be still more useful as antispasmodics.

Other antispasmodics, instead of lessening the irritability of nerve-centres, may **paralyse** the structures through which the nerves act. Thus, nitrite of amyl appears to arrest the spasm of the vessels in angina pectoris, by causing paralysis of the vessels themselves or of the peripheral ends of the vaso-motor nerves.

Adjuvants.—As spasm is usually an indication of deficient nervous power, tonics, as quinine, iron, cod-liver oil, arsenic, sulphur, cold baths, and moderate exercise, are useful as adjuvants.

It has already been mentioned, that a healthy condition of the various parts of the body depends on proper nutrition and proper removal of waste. Therefore, when there is a tendency to spasm, the diet should be plain, but nutritious. Those conditions which tend to cause excessive waste should be avoided, such as exciting emotions, excessive bodily or mental work, a close atmosphere, and late hours. Attention must be paid also to the proper removal of all waste, by the use of purgatives, cholagogues, or diuretics if necessary.

Great irritability of the nervous system is usually observed in gouty subjects before an attack of gout comes on. It is uncertain to what this irritability is due, but it may not improbably be caused by the retention within the body of the products of tissue-waste. Some years ago there was considerable discussion regarding the active ingredient of bromide of potassium, some attributing its antispasmodic action to the bromine, and others to the potassium. It occurred to me that possibly its action might be partly due simply to its action as a saline leading the patient to drink more water, and thus assisting the elimination of the products of tissue-waste. I accordingly tried 30-grain doses of chloride of sodium in cases of epilepsy. In some it did little or no good, but in a few it appeared to have nearly as powerful an action as bromide of potassium.

Uses.—Antispasmodics are used in convulsive diseases.

The antispasmodics used in hysteria may be divided into substances which exert on the higher nerve-centres a sedative, tonic, or stimulant action, thus :

I. Sedatives	Alkaline bromides.	
II. Tonics	Zinc salts.	
III. Stimulants, which have a powerful odour, and probably act on the higher centres through the olfactory organs, either by direct application or during their elimination (p. 41).	Musk Castor	Derived from the genital organs of animals.
	Sumbul Valerian	Similar in the nature of their odour to the above, though derived from plants.
	Asafœtida Ammoniacum Galbanum	Containing sulphur oils.

In epilepsy, laryngismus stridulus, and infantile convulsions, bromides of potassium, sodium, ammonium, and calcium, nitrite of sodium, salts of silver, zinc, and copper.

In chorea, arsenic, conium, the salts of copper and zinc.

In spasmodic asthma, lobelia, stramonium.

In spasm of the blood-vessels, nitrite of amyl and other itrites.

Action of Drugs on the Cerebellum.

The chief function of the cerebellum appears to be the maintenance of equilibrium. Symmetrical lesions on both sides of the organ or division of it down the centre from before backwards, cause very little disturbance of the equilibrium, but when a lesion is unsymmetrical the equilibrium is disordered.

According to Ferrier, if the lesion affects the whole of a lateral lobe, there is a tendency for the animal to roll over towards the affected side. In an animal standing on all fours or lying on the ground, we regard the centre of the back as the point of movement, but in a man standing upright we usually take the face, and therefore what we should regard in an animal as rolling towards the affected side, would be equivalent in man to a rotation towards the sound side. If the lesion is limited to one part of the lateral lobe, it may not cause rotation, but only falling towards the opposite side. When the anterior part of the middle lobe of the cerebellum is injured, the animal tends to fall forward, and in walking usually stumbles, or falls on its face. When the posterior part of the middle lobe of the cerebellum is injured, the head is drawn backwards and there is a continual tendency to fall backwards when moving.[1]

Injuries of the cerebellum are frequently associated with a certain amount of nystagmus, and in all probability the complete or partial inability to walk or stand which alcohol produces, is due to its action on the cerebellum.

Different kinds of spirit appear to have a tendency to affect different parts of the cerebellum, for good wine or beer is said to make a man fall on his side, whisky, and especially Irish whisky, on his face, and cider or perry on his back.[2] These disturbances of the equilibrium correspond exactly with those caused by injury to the lateral lobes, and to the anterior and posterior part of the middle lobe of the cerebellum respectively. Apomorphine in large doses appears also to have an action on the cerebellum or corpora quadrigemina, as the animal poisoned by it does not vomit, but moves round and round in a circle.

The action of alcohol on frogs is peculiar and differs from that of other narcotics, inasmuch as it appears to affect unequally the two sides of the nervous apparatus by which the equilibrium is maintained, so that in a certain stage of alcohol-poisoning they excite similar *manège* movements to those which occur after division of the corpora quadrigemina on one side.[3]

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[1] Ferrier, *Functions of the Brain*, p. 94.

[2] Shorthouse, Baily's *Magazine of Sports*, 1880, vol. xxxv. p. 396.

[3] Wilhelm Wundt: *Untersuchungen zur Mechanik der Nerven und Nervencentren.* Zweite Abtheilung, 1876. Stuttgart.

CHAPTER IX.

ACTION OF DRUGS ON THE ORGANS OF SPECIAL SENSE.

Action of Drugs on the Eye.

Action on the Conjunctiva.—Before light can reach the retina, it has to pass through the cornea, which is covered by epithelium continuous with that of the conjunctiva. Alterations in either or both of these textures are therefore very important in regard to the integrity of vision. The chief drugs employed in the local treatment of diseases of the cornea and conjunctiva are warmth, moist and dry, anæsthetics, anodynes, antiphlogistics, antiseptics, and astringents. The chief **astringents** are perchloride of mercury, oxide of mercury, and nitrate of silver. The chief **antiseptics** are perchloride of mercury, quinine, boric acid, and sulphocarbolate of sodium. The chief **sedatives** are hydrocyanic acid, opium, belladonna, atropine, and cocaine. There are two astringents in common use which ought to be avoided, these are solutions of lead and of alum. Lead salts are objectionable, because if there is any ulceration on the cornea they may form an insoluble albuminate and cause permanent opacity. Salts of alum are said by Tweedy to be perhaps still more objectionable, because alum has the power of dissolving the cement by which the fibrillæ of the cornea are held together, and this is very apt to give rise to perforation of the cornea whenever the epithelium is removed by injury or inflammation. Tweedy also thinks that strong solutions of common salt, ten per cent. or more, and solution of permanganate of potassium also dissolve the corneal cement and should therefore be avoided in inflammation of the conjunctiva or of the cornea. He considers that sulphate of zinc should be avoided, for the same reason, but it is largely used by others. The best astringent is probably perchloride of mercury, $\frac{1}{64}$th to $\frac{1}{16}$th of a grain to an ounce of water, and coloured with cochineal. The next best is an aqueous solution of boric acid, containing 3 to 8 grains of it with 3 to 10 grains of sulphocarbolate of sodium per ounce.

The chief effects which drugs produce on the eye, besides those just described, are alterations in the size of the pupil, in

the power of accommodation, in the intra-ocular pressure, in the sensitiveness of the retina to impressions, and in the apparent colour of objects.

Action of Drugs on the Lacrimal Secretion.—The great power of certain volatile oils, such as those of onion or mustard, to irritate the eyes and cause secretion of tears is well known. The prolonged action of atropine diminishes the secretion. Eserine abolishes the action of atropine, and quickly increases the secretion.[1]

Projection of the Eyeball.—The non-striated muscular fibres which are contained in the orbital membrane and in both eyelids push the eyeball forward and draw the eyelids back when they contract. Like the dilator pupillæ they are innervated by the sympathetic, and consequently some degree of protrusion of the eyeball is frequently produced by such substances as dilate the pupil, and especially by cocaine. Excessive pain, or an asphyxial condition of the blood, has a powerful action in producing this effect, so that in men subjected to torture in the Middle Ages protrusion of the eyeballs was noticed; and both in animals and men dying from rapid asphyxia the eyeballs may seem as if starting from the head.

Action on the Pupil.—The iris is usually said to consist of two muscles, the sphincter, which has circular fibres and contracts the pupil, and the dilator, which has radial fibres and dilates the pupil. All observers are agreed regarding the sphincter muscle of the eyes, but some deny the existence of the dilator muscle. In the following description, however, I shall take the view which is usually accepted.[2]

The sphincter receives its motor nervous supply from the third nerve, and the dilator from the cervical sympathetic. The nervous centre for the contraction of the pupil probably lies in the corpora quadrigemina; the nerve-centre for the dilatation of the pupil lies in the medulla oblongata, but there seems to be another dilating centre, situated in the floor of the front part of the aqueduct of Sylvius.[3] The contracting nerves are contained in the third nerve, and pass to the ciliary ganglion, and thence to the eye. Along with them motor fibres pass also to the ciliary muscle. This muscle when contracted lessens the tension of the suspensory ligament on the lens, allowing the latter to become

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[1] Maynard, *Virchow's Archiv*, vol. lxxxix. p. 258.

[2] At present it is generally assumed that muscular fibres, either voluntary or involuntary, contract only in the direction of their length. If we suppose that they can contract either in the direction of their length or their width, the movements of the iris might be more readily explained. At present we assume the presence of a dilator muscle, which is almost certainly absent in many animals, in order to explain phenomena which might be explained just as readily by the supposition that the muscular fibres which are present can contract in two directions (see p. 117).

[3] Foster's *Physiology*, 4th ed.

more spherical, and thus accommodating the eye for near objects. Such accommodation and contraction of the pupil generally accompany one another. The arrangement of the nerves of the eye is very diagrammatically shown in Fig. 74. A few of the dilating fibres are contained in the fifth nerve, but most of them pass down the spinal cord to the cilio-spinal region in the lower cervical and upper dorsal part of the cord, and thence through the second dorsal nerve in monkeys and probably in man, or through the inferior cervical and superior dorsal nerves in the rabbit, into the cervical sympathetic, in which they again ascend to the eye.

FIG. 74.—Diagram to show the nervous supply of the eye. *a*, nerves to the ciliary muscle regulating accommodation; *b*, nerves to the contracting fibres, and *c*, nerves to the dilating fibres of the iris; *d*, vaso-motor nerves to the vessels of the eye. The iris is put apparently behind instead of in front of the lens for convenience in showing the passage of nerves to it.

Along with the dilating fibres others pass to supply the orbital muscle at the back of the orbit, which causes protrusion of the eyeball, as already mentioned. There are also other fibres from the sympathetic (vaso-motor) which supply the muscular coats of the arteries of the ciliary vessels.

The dilating centre may be stimulated directly by venous blood circulating in it. In consequence of this the pupils usually dilate much when the respiration is imperfect, as during dyspnœa; but when the asphyxia becomes complete the centre again becomes paralysed and the size of the pupil diminishes. It may be stimulated reflexly by irritation of sensory nerves, so that dilatation of the pupil has been used as an indication of sensation in animals paralysed by curare. It seems to be readily stimulated by irritation of the genital organs. This is probably the reason why dilatation of the pupil frequently occurs in persons suffering from irritation of the genital organs. It is probably also readily stimulated by irritation of the intestinal canal, and such irritation may be the cause of dilatation of the pupil in children suffering from worms, and in cases of poisoning by drugs which irritate the gastro-intestinal canal, like aconite.

The drugs which act upon the iris are divided into two classes: **Mydriatics** which dilate, and **Myotics** which contract the pupil. The most important of these are such drugs as have a local action

on the eye, and they alone are used in ophthalmic medicine. They are indicated in the following list by an *.

Mydriatics.	Myotics.
General anæsthetics—chloroform, ether, &c.	General anæsthetics—chloroform, ether, &c.
*Atropine.	*Calabar bean.
*Belladonna.	
Belladonnine.	
Benzoyltropine.	
Cocaine.	
Daturine.	
*Duboisine.	
Gelsemine locally.	Gelsemine internally.
*Homatropine (oxytoluylic-acid-tropine).	Jaborandi.
	Lobeline internally.
Hyoscyamine.	Morphine internally.
Muscarine locally (?).	Muscarine internally.
	,, locally.
Narcissine.	Nicotine locally.
Piturine.	Opium.
Scopalein.	*Physostigmine (eserine).
Stramonium.	Pilocarpine.
	Thebaine.

Anæsthetics occur in both classes, because they cause contraction towards the commencement of their action, while later on they cause dilatation. The probable reason of this is that at first they lessen reflex action, so that the reflex dilatation of the pupil by stimulation of sensory nerves is abolished. Later on, when they begin to paralyse the respiration, the accumulation of venous blood causes irritation of the dilating centre and widens the pupil. Dilatation of the pupil during the administration of anæsthetics is therefore to be regarded as a sign of imperfect aëration of the blood, due either to embarrassed or failing respiration (p. 218) or failing circulation (p. 207).

The contraction caused by morphine is also central, and probably due to a similar cause.

It is possible that the local application of drugs to the eyes may have an action on the pupil due merely to their effect as irritants, and independent of any special action on the iris, for E. H. Weber [1] found that local irritation at the margin of the cornea causes partial dilatation. Irritation in the middle of the cornea causes rather contraction of the pupil. Localised irritation at the margin of the iris may cause dilatation at that part.

The reason why muscarine has been found by Ringer and

[1] Quoted by Landois, *Physiologie*, 1880, p. 799.

Morshead to dilate the pupil when applied locally is probably that the solution they used was very irritating, either from its strength or for some other reason, while Schmiedeberg and Harnack found it to contract the pupil both when given internally and applied locally.

The contraction of the pupil noticed by Rossbach in rabbits immediately after the application of atropine, may also have been due to local irritation. The occurrence of dilatation in one case and of contraction in the other may possibly have been due to the solution being dropped into the eye in a different way in the two cases.

The commonest and most important **local mydriatic** and **myotic** are respectively atropine and physostigmine (eserine).

From ten to twenty minutes after a solution of atropine has been dropped on the eye, the pupil dilates and the ciliary muscle becomes paralysed, so that the accommodation for near objects is no longer possible, and the eye remains focussed for distant objects. When a solution of physostigmine is dropped into the eye, the pupil contracts and the ciliary muscle becomes spasmodically contracted, so that the eye is accommodated for near objects.

It is very difficult to explain the **mode of action** of these drugs satisfactorily, and authorities are by no means agreed regarding it. That the action is local is shown by the fact that when either atropine or physostigmine is applied to one eye its action is limited to it and the other remains unaffected. If care be taken to limit the application of a solution of atropine to one side of the margin of the cornea, local dilatation of the corresponding part of the pupil may be produced.

Dilatation of the pupil may be due to

(1) Paralysis of the sphincter, or

(2) Excessive action of the dilator, or

(3) Both conditions combined.

Paralysis of the sphincter may be due to (*a*) imperfect action or paralysis of the oculo-motor centre in the corpora quadrigemina, (*b*) to paralysis of the ends of the third nerve in the sphincter iridis, or (*c*) to the action of the drug upon the muscular fibres of the sphincter itself, or to a combination of two or more of these factors.

Along with the factors just mentioned might be associated excessive contraction of the dilator muscle, which may be due to stimulation (1) of the sympathetic centre in the medulla, (2) of the ends of the sympathetic in the dilator muscle, or (3) of the dilator muscle itself.

Excluding for the present the question of excessive action of the dilator muscle and confining ourselves to the causes of paralysis, we see that paralysis of the cerebral oculo-motor centre as a factor in dilatation of the pupil by atropine is excluded by the local action of the drug, by the experiments of Bernard and

others, which show that dilatation occurs from the local action of atropine when the ciliary ganglion is extirpated and all the nerves of the eye have been divided, and by the mydriatic action of atropine even in the exsected eye. We can now limit its action either to paralysis of the ends of the oculo-motor nerve, or paralysis of the muscular fibres of the sphincter.

That the ends of the oculo-motor nerve in the sphincter iridis are paralysed is shown by the experiment that when the pupil is under the full action of atropine, irritation of the third nerve will not produce any contraction in it, although the sphincter will still contract when stimulated directly.

Here also we find the same relation between the action of atropine on nerves supplying striated and non-striated muscle that we have already noticed in the case of the œsophagus (p. 139), for in most animals the iris consists of unstriated muscular fibre, and atropine causes dilatation; but in birds the iris consists of striated muscular fibre, and atropine causes no dilatation. Paralysis of the ends of the oculo-motor nerve in the iris itself may be looked upon as one of the factors in dilatation by atropine, and similar paralysis of the fibres supplying the ciliary muscle may be regarded as the cause of loss of accommodation.

In addition to this, however, when the dose of atropine is large, the muscular fibres of the sphincter themselves become paralysed, and fail to contract even when directly irritated.

The question now arises whether in addition to paralysis of the oculo-motor nerve there is not also excessive action of the dilator muscle. That such action of the dilator is actually present appears to be shown by the following fact, viz. that the dilatation caused by atropine does not appear to be merely passive, but occurs with such force as to tear the iris away from the lens, and break down inflammatory adhesions which may have formed between them. This conclusion has been considered to be supported also by the facts :—(*a*) That when the oculo-motor nerve is divided the pupil does not dilate nearly to the same extent as it does from the application of atropine. This is shown both by a comparison of measurements of the eye under the two conditions and by the observation that after the nerves have been divided and partial dilatation produced, atropine causes the pupil to dilate still more. And similarly in dilatation due to paralysis atropine increases the mydriasis. (*b*) When the pupil is dilated by atropine, section of the sympathetic in the neck lessens the dilatation.

We may consider, then, with tolerable certainty, that dilatation caused by atropine is due to increased action of the dilator as well as diminished action of the sphincter muscles of the iris.

Contraction of the pupil may be due to

(1) Excessive action of the sphincter, or

(2) Paralysis of the dilator.

That the contraction caused by physostigmine is not due to paralysis of the dilator is shown by the pupil dilating somewhat when shaded, even when the drug is exerting a well-marked action. Excessive action of the sphincter must therefore be regarded as the cause of the myosis. Such action may be due to stimulation (1) of the oculo-motor cerebral centre, (2) of the ends of the oculo-motor nerve in the sphincter, or (3) to increased action of the muscular fibres in the sphincter from the direct effect of the drug upon them. The local action of physostigmine upon the eye excludes the cerebral centre, and leaves for our consideration stimulation of the ends of the nerves and of the muscular fibres themselves.

These two structures seem to be specially affected by different drugs—so that **local myotics** may be divided into two classes—

1st. Those which act upon the peripheral ends of the oculomotor nerve.

2nd. Those which affect the muscular fibre of the sphincter iridis.

The first class includes muscarine, pilocarpine,[1] and nicotine, whereas physostigmine belongs to the second.

Muscarine, pilocarpine, and nicotine, when applied to the eye, cause contraction of the pupil and spasm of accommodation. Atropine, as we have already seen, not only paralyses the ends of the oculo-motor nerve, which these drugs stimulate, but has also an action on the muscular fibre itself. Its subsequent application will therefore remove the effect of these drugs, and they will not act when atropine has been applied first. As physostigmine stimulates the muscular fibre itself, it will cause contraction in an eye which is dilated by atropine unless the action of the atropine has been carried to such an extent as to paralyse the muscular fibre.

The contraction produced by muscarine in the eye of the cat is so great as to reduce the pupil to a mere slit, and is much greater than that caused by physostigmine, for muscarine, acting only on the ends of the oculo-motor, produces spasm in the sphincter without affecting the dilator, while physostigmine, acting on the muscular fibres, is said to stimulate those of the dilator as well as the sphincter, and thus to render the contraction less complete.[2]

It has already been pointed out, however, that the action of atropine is not confined to the ends of the oculo-motor nerve, but affects the muscular fibre itself, and thus it will counteract the effect of physostigmine, which it would not do if it acted only on the nerves.

Atropine consists of the combination of a base, tropine, with

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[1] Schmiedeberg, *Arzneimittellehre*, p. 71. [2] Schmiedeberg, *op. cit.*

tropic acid. Tropine itself has no mydriatic action, but when an atom of hydrogen in it is displaced by an acid residue it acquires this action. A number of combinations of tropine with different acids have been artificially prepared by Ladenberg, who terms them tropeïnes. Amongst these are homatropine, in which the tropine is combined with oxytoluylic acid, and also benzoyl-tropine. Atropine appears to be identical with daturine. Hyoscyamine is also a combination of tropine with tropic acid, but it appears to be only isomeric with and not identical with atropine, though it seems to be identical with duboisine.

Action of Drugs on Accommodation.—The accommodation of the eye depends upon the ciliary muscle. When the eye is at rest the lens is flattened by the elastic tension of the zonule of Zinn. During accommodation for near objects the ciliary muscle draws the zonule forward and allows the lens to become more convex. The ciliary muscle is innervated by the third nerve: the centre for it appears to be in the posterior part of the floor of the third ventricle. Those drugs which affect the iris, also affect the power of accommodation. Their action on the iris and on accommodation do not, however, always begin at the same time, nor have they the same duration. The action of physostigmine and atropine on accommodation usually begins after, and passes away long before, the affection of the pupil.

Action on intra-ocular pressure.—The intra-ocular pressure depends greatly on the amount of fluid contained in the vitreous, and this in turn is determined by two factors :—

(1) The amount of fluid secreted by the ciliary body.

(2) The freedom with which fluid escapes at the angle of the anterior chamber.

The aqueous humour and the fluid which nourishes the vitreous and crystalline lens are chiefly secreted by the ciliary processes. It ultimately passes out from the anterior chamber of the eye by a number of small openings (*f*, Fig. 75) close to the junction of the cornea and iris into the canal of Schlemm (*c, s*, Fig. 75), thence into the anterior ciliary veins. Some of it also passes into the perichoroidal space, and out through the lymphatics.

The intra-ocular pressure may be increased by (*a*) more rapid secretion from the ciliary processes, or (*b*) interference with its outward flow from the eye, or (*c*) by increased quantity of blood in the vessels of the iris. It may be diminished by the contrary conditions.

More rapid secretion from the ciliary process probably takes place under nervous conditions which are not at present well known. Interference with the flow of the aqueous humour out of the anterior chamber may occur in aquo-capsulitis, in which the openings from the anterior chamber into the spaces of Fontana are occluded by a coating of inflammatory lymph ; also

in glaucoma where these openings are shut by the iris being pressed forward against the cornea, as in Fig. 75, and in iritis where the iris is much congested and the communication between the posterior and anterior chambers is interrupted by complete adhesion of the pupillary edge of the iris to the anterior capsule of the lens (total posterior synechia). The secretion is probably diminished by the action of atropine. In glaucomatous states where the periphery of the iris lies in contact with the cornea the outward flow through the spaces of Fontana may often be increased by Calabar bean, which, by causing contraction of the circular fibres of the iris, flattens the arch of the iris and, drawing it away from the cornea, reopens the contracted angle between the cornea and iris, and permits the passage of fluid through the spaces of Fontana.[1]

There are few or no experiments on the tension in the vitreous humour of the eye, though by the term intra-ocular tension is usually intended the pressure in the vitreous humour. The

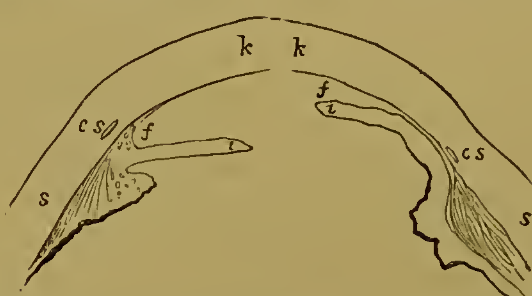

FIG. 75.—This diagram (which I owe to the kindness of Mr. J. Tweedy) represents a section through the corneo-scleral region, ciliary body and iris, of a healthy eye (left side), and of a glaucomatous eye (right side): *k*, cornea; *s*, sclerotica; *i*, iris; *f*, spaces of Fontana; *c s*, canal of Schlemm. In the glaucomatous eye the ciliary body is atrophied, and the iris lies against the cornea, preventing the escape of fluids through the spaces of Fontana and canal of Schlemm.

degree of intra-ocular tension is usually ascertained by pressing the finger *secundum artem* upon the eye and observing whether it is harder or softer than usual, or by pressing upon the sclerotic with an ivory point attached to a registering spring, and noticing the pressure required to produce an indentation. These methods of experiment are valuable clinically, but the tension can be more exactly ascertained in animals by passing a small trocar into the anterior chamber and connecting it with a manometer. The results of experiments even by this method are not entirely in accordance. The most recent ones by Graser [2] appear to show that the tension depends to a great extent upon the height of the blood-pressure generally: contraction of the pupil diminishes, and dilatation increases the intra-ocular tension. Eserine causes temporary increase at first, but after contraction of the pupil comes on, the tension is diminished. Atropine in doses sufficient

[1] J. Tweedy, *Practitioner*, Nov. 1883, vol. xxxi. p. 321.
[2] Graser, *Archiv f. exp. Path. u. Pharm.*, Bd. xvii. Heft 5.

to dilate the pupil increases the tension. The precise effect of atropine on intra-ocular tension in man is disputed. From clinical observation the truth would seem to be that in a perfectly healthy eye and in ordinary iritis atropine and other mydriatics diminish tension, whereas they increase the tension when the anterior chamber is shallow from narrowing of the iridic angle. In glaucomatous states atropine and other mydriatics almost always rapidly increase tension. This action of atropine and its allies not only makes them dangerous in cases of glaucoma, but where this disease has been impending it has been at once brought on by their use. From its power to diminish tension eserine is useful in glaucoma.

Uses of Mydriatics and Myotics.—Belladonna is employed locally for its sedative action, to relieve pain and allay irritation and inflammation in the conjunctiva, cornea, choroid, or iris.

Mydriatics and myotics are used not only for their action upon the pupil but for their action upon accommodation and intra-ocular pressure.

Mydriatics are employed to dilate the **pupil** for the purpose of facilitating ophthalmoscopic examination, assisting the detection of cataract commencing in the periphery of the lens, or allowing the patient to see past the edge of a cataract or corneal opacity when this is central in position, and obstructs the vision with a pupil of normal size. They are used to prevent prolapse of the iris, or to restore it to its normal position when already prolapsed in cases of perforating ulcer or mechanical lesion of the cornea. They are employed in iritis to afford rest to the inflamed tissues of the eye, and to keep the iris as far as possible off the surface of the lens and prevent adhesions of its posterior surface to the anterior surface of the lens.

Mydriatics are employed to paralyse the ciliary muscle, and thus destroy the power of **accommodation** in order to test the condition of the refractive media of the eye in cases of astigmatism, or in cases where the patients either suffer from spasm of the ciliary muscle or are unable voluntarily to relax the accommodation.

Myotics are used to counteract the effect of mydriatics which have been previously employed, or in mydriasis following a blow or paralysis of the third nerve. They are used also to counteract deficiency in tone of the ciliary muscle, as in paralysis of accommodation consequent on diphtheria, asthenopia, a blow on the eye, &c.

Myotics are useful in cases of threatening and commencing glaucoma and often even in more advanced cases of glaucoma, from their power to lessen intra-ocular tension. As a temporary expedient they are often of the greatest service in cases of acute glaucoma. So, also, if perchance the instillation of atropine have induced glaucoma, myotics will not only counteract the

mydriasis, but often rapidly restore the intra-ocular tension to the normal standard.[1]

Mydriatics and myotics may be employed alternately in order to ascertain the presence of any adhesions of the iris, and to break them down if present.

In glaucoma the intra-ocular tension within the anterior chamber is greatly increased, and the increase, according to Tweedy, is due to the natural channel of escape for the aqueous humour through the spaces of Fontana and the canal of Schlemm being obstructed by the iris lying against the cornea. This condition is relieved by myotics, which, by causing contraction of the pupil, draw the iris away from the cornea, and thus allow the fluid to escape through the spaces of Fontana. When the anterior chamber of the eye is shallow and the iris is lying close to the cornea, so as nearly, though not quite, to obstruct the spaces of Fontana, atropine may induce an attack of glaucoma by dilating the pupil and thus packing the tissue of the iris into the angle between it and the cornea, so as to render the obstruction to the spaces of Fontana complete.

Action of Cocaine.—Cocaine, when applied locally to the eye, has several actions. It produces local anæsthesia, dilatation of the pupil, and relaxation with more or less complete paralysis of the ciliary muscle. When two to three drops of a 4-per cent. solution are applied to the eye at intervals of five minutes, such complete local **anæsthesia** of the cornea, conjunctiva, and iris is produced in twenty to thirty minutes as to allow operations to be performed on the eye. At the same time the cocaine causes constriction of the superficial vessels, producing blanching of the conjunctiva. The **dilatation** of the **pupil** is great, is quickly attained, and differs from that produced by atropine in the fact that the cocainised pupil reacts to light and accommodation. The mydriasis is probably due to stimulation of the ends of the sympathetic in the iris, for cocaine will not produce any mydriatic effect after the cervical sympathetic has been cut for such a length of time as to allow degeneration of the peripheral ends to occur, nor has stimulation of the cervical sympathetic any effect in increasing the *ad maximum* cocaine mydriasis. That the third nerve is not paralysed is shown by the fact that stimulation of it produces contraction in the cocainised pupil. A similar effect follows local stimulation of the sphincter pupillæ. That the action of cocaine is exerted on the peripheral ends and not on the centres of the sympathetic is shown by the fact that section of the cervical sympathetic does not alter the pupil which is fully dilated by cocaine, and cocaine induces mydriasis in an exsected eye.[2]

Action of Drugs on the Retina.—By a comparison of the retina of a frog kept in darkness with one exposed to light, it has

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[1] Tweedy, *loc. cit.*

[2] Jessop, *Proc. Roy. Soc.*, 1885.

been found that light causes not only the internal segments of the cones [1] and rods [2] but also the pigment-cells of the retina to contract, so that the external parts of the rods and cones as well as the pigment are drawn away from the external towards the internal limiting membrane of the retina (Fig. 76*b*). A similar effect is produced by heat.[2] The retina of a frog which has been tetanised by strychnine in complete darkness has an appearance

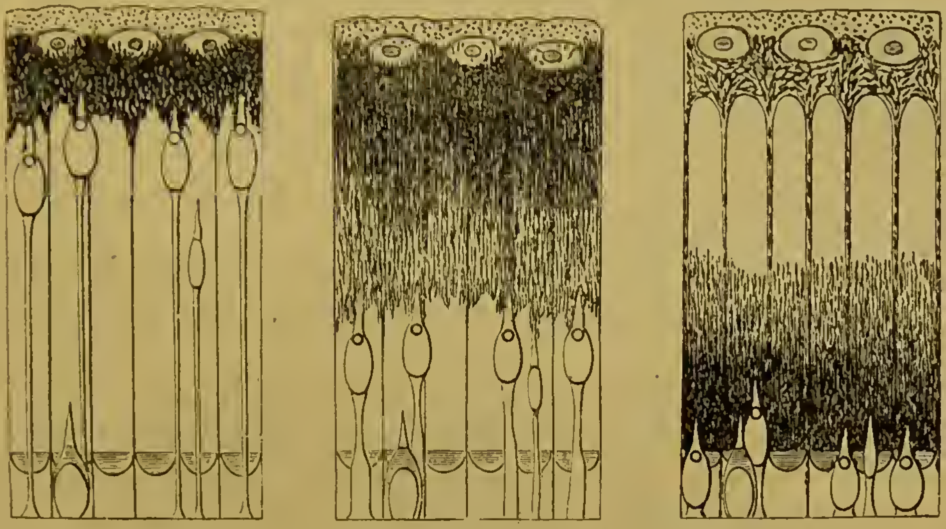

FIG. 76.—Shows the position of the rods and pigment-cells in the retina of the frog: *a*, after the animal has been kept in complete darkness for one or two days; *b*, after it has been exposed to diffused daylight for five or ten minutes, after being kept in darkness for twenty-four hours; *c*, after exposure to light as in *b*, but for half an hour instead of a few minutes. This also represents the position of the rods and pigment-cells in strychnine tetanus.

similar to that of a retina which has been exposed to full daylight, the strychnine having caused extreme contraction of the rods, cones, and pigment-cells (Fig. 76*c*). A similar effect is produced by tetanising the eye itself either by induced currents in the dark, or while it is still in the head or immediately after its excision. Curare neither hinders this action nor produces it.

Action of Drugs on the Sensibility of the Eye.—The sensitiveness of the eye to impressions is increased by strychnine, the field of vision becoming larger, and the sight more acute, so that objects can be distinctly observed at a greater distance, and the field of colour is increased for blue. This action appears to be to a certain extent local, as it occurs more distinctly on that side where the strychnine has been injected hypodermically. The sense of colour is affected in a remarkable way by santonin, which at first causes objects to appear somewhat violet and afterwards of a greenish-yellow. The yellow colour has been ascribed to staining of the media of the eye by santonin, as it becomes yellow when exposed to the light; others again have supposed

[1] Engelmann (and von Genderen Stort), *Pflüger's Archiv*, xxxv. p. 498.
[2] Gradenigo, jun., *Allg. Wiener med. Ztg.*, 1885, No. 29.

the alteration in the apparent colour of objects to be due, first to a stimulation, and then to a paralysis of those constituents of the retina by which the violet colour is perceived.

The sensibility of the eye for red and green appears to be sometimes diminished by physostigmine.

Action of Drugs in Producing Visions.—It may be well here to mention the effect of some drugs in causing subjective sensations of sight, although these probably depend rather upon the action of the drugs on the brain, than on the eye itself. The centres for sight, according to Ferrier, are the angular gyrus (14 and 15, Fig. 68, p. 185), and the occipital lobes. In delirium tremens arising from alcoholic excess the patients often complain much of visions of the most disagreeable character, which often take the form of demons or of animals.

Cannabis indica produces in some persons, though not in all, visions which may be pleasant or laughable. These chiefly occur just before sleep.[1]

Salicylate of sodium in some persons tends to cause most disagreeable visions whenever the eyes are shut, and I have seen it have this effect even in such a small dose as five grains. Large doses of digitalis may cause subjective sensations of light, and after taking nearly one grain of digitalin in the course of forty-eight hours I suffered from the centre of the field of vision being occupied by a bright spot surrounded by rainbow colours. Digitalin when introduced into the eye locally causes at first smarting and lacrimation, which soon passes off, but after four or five hours, when a light is looked at, a halo is seen surrounding it, which is not improbably due to some opalescence in the cornea.[2]

Toxic Amblyopia.—Belladonna taken internally in sufficient quantity causes dilatation of the pupil and misty vision. Alcohol, tobacco, quinine, and lead all cause failure of the power of vision for form and for certain colours, as well as limitation of the field of vision either in the centre or the periphery. These symptoms are at first functional, but if not relieved they may be the precursors of actual anatomical changes.

Action of Drugs on Hearing.

The sense of hearing depends on the transmission of sonorous vibrations from the air to the auditory nerve by means of the membrana tympani and the ossicles of the ear, and upon the perception of those vibrations by the brain.

The centre for hearing, according to Ferrier, is in the

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[1] Compare Schroff, *Pharmacologie*, 4th ed. p. 535, and Wood, *Materia Medica*, 3rd ed. p. 236.

[2] Lauder Brunton, *On Digitalis*, &c.

superior temporo-sphenoidal convolution (16, Fig. 68, p. 185). It is probable that subjective sounds not depending on disturbance of the auditory apparatus, such as the sounds of voices, &c., heard in delirium or mania, or as the prodromata of an epileptic fit in certain individuals, or during intoxication by cannabis indica, are due to irritation of these centres.

The sense of hearing may be dulled by any interference with the passage of the sound into the ear, as by wax in the auditory meatus, by disease of the auditory nerve or of the brain itself.

The hearing may be rendered more acute by the removal of any obstacle in the way of transmission of sound to the auditory nerve, or by drugs which increase the excitability of the auditory nerve or of the brain; thus the wax may be removed by simply syringing; thickness and catarrh of the Eustachian tube which interfere with vibrations in the middle ear may be lessened by the inhalation of camphor and ammonia, or by the application of a solution of ammonium chloride and sodium bi-carbonate to the posterior nares either by the spray or nasal douche. The excitability of the auditory nerve or of the brain is increased by strychnine, which renders the hearing more acute.

Subjective noises in the ear, such as humming, buzzing, or ringing, are often very troublesome. Bubbling noises may be due to mucus in the Eustachian tube. Buzzing or humming are probably generally caused by vascular congestion either of the external meatus, of the middle ear, or of the Eustachian tube. Where the bubbling noises are due to the presence of mucus they may be to a considerable extent removed by washing out the mucus with a solution of carbonate of sodium applied by a nasal douche. Noises in the ears due to hyperæmia may be lessened or removed by cholagogue purgatives and by hydrobromic acid. Where chronic thickening of the membrane is present, relief is usually afforded by iodide of potassium or iodide of ammonium, both applied locally and taken internally. Subjective noises in the ears are caused by quinine in large doses, and also by salicylate of sodium. Both of these drugs have their effect upon the ear to a great extent neutralised by hydrobromic acid, and ergot[1] is said to have a similar power to prevent or remove the unpleasant singing. It is uncertain whether the singing caused by quinine and salicylates is due to their action on the auditory apparatus, or the cerebral centres; but the fact that in larger doses they may cause delirium indicates that even the earlier symptom of buzzing in the ears may be due, in part at least, to their action on the cerebral centres.

[1] Schilling, *Aertzl. Intelligenzblatt*, 1883.

Action of Drugs on Smell.

Many drugs, such as musk and ethereal oils, have a marked and characteristic smell, due to their effect upon the terminal branches of the olfactory nerve. This nerve is soon exhausted, so that in a very short time the smell is no longer perceived with anything like the intensity it was at first. Such smells as these just mentioned cannot be perceived by persons suffering from anosmia, but certain drugs, such as ammonia or acetic acid, can be recognised by them. The reason of this is that although such persons are incapable of perceiving any true smell, the nasal branches of the fifth nerve are irritated by pungent vapours, and thus produce a certain kind of sensation. The power of distinguishing smells seems to be increased by strychnine; which appears at the same time to render such disagreeable odours as those of asafœtida, garlic, and valerian agreeable. This effect may be due to the action of strychnine on the olfactory apparatus, but it is very probably due rather to the action of the drug on the cerebral centre for smell, which, according to Ferrier, is situated at the tip of the temporo-sphenoidal lobe. The power to distinguish smells is diminished by such drugs as lessen the sensibility of the brain, or by those which cause alterations in the nasal mucous membrane, as, for example, iodide of potassium given in such doses as to produce coryza.

Action of Drugs on Taste.

Most of the substances used in medicine have a strong taste, and many a very unpleasant taste.

What is usually termed taste frequently depends on a mixture of taste and smell, and if the sense of smell is abolished for the time being, the characteristic taste of the substance cannot be distinguished. This is the reason why castor-oil, which owes its nauseous taste almost entirely to its odour, can be swallowed without being so readily distinguished if the nose is held during the act of swallowing. In addition to the taste they produce in the mouth, certain substances leave an impression termed 'after taste' on the tongue after they have been swallowed or ejected; and this is sometimes quite different from that of the taste of the substance itself: thus bitters leave a sweet after-taste in the mouth. If quinine is taken in a nearly neutral solution, it leaves a persistent bitter taste from the sparingly soluble alkaloid being precipitated on the tongue and remaining there for a length of time, but if the quinine be taken with excess of acid, so as to keep it entirely in solution, and washed out of the mouth immediately with a draught of water, it leaves a sweet after-taste.

Some substances after their entrance into the blood are excreted by the saliva and may cause a somewhat persistent taste in the mouth; this is observable in the case of iodide of potassium.

Iodine appears also to have the power of causing other substances to be excreted by the saliva, when they are combined with it, and thus Bernard found that iodide of iron was secreted by the saliva, though lactate of iron was not; and I have sometimes thought that iodine has a similar effect upon quinine, because I have very frequently noticed patients complain of a persistent bitter taste in their mouth when I have given quinine combined with iodide of potassium, although they did not complain of this when either of the drugs has been given without the other.

CHAPTER X.

ACTION OF DRUGS ON RESPIRATION.

Respiratory Stimulants and Depressants.

It is usually supposed by naturalists that in the descent of man from some organism low in the scale of existence, he has passed, at a remote period, through a stage resembling the Ascidians or Tunicata. In these animals respiration is maintained by water being driven through a perforated sac in the meshes of which the nutritive fluids of the animal circulate. The contractile motions of the sac by which the circulation of fluid is maintained probably depend on a **nervous ganglion** situated between the oral and anal apertures as represented in the diagram (Fig. 77). We do not know whether or not this ganglion may influence the circulation which is maintained by the rhythmical contractions of the simple tube which serves as a heart. These drive the fluid first in one direction, and then after a while the action of the tube is reversed, and its contractions drive the fluid in the opposite direction. This ganglion in its functions would correspond with the **medulla oblongata** in the vertebrata, and thus the medulla oblongata may be looked upon as a lower and more **fundamental centre** than the brain or spinal cord.

We see this more distinctly perhaps by looking at the two diagrams (Figs. 78 and 79) representing an amphioxus and a fish. In the amphioxus respiration is kept up in much the same way as in the ascidian, the water passing from the pharyngeal to the atrial sac and through the atrial aperture or abdominal pore. There is no head and no organs of special sense, and so we have no brain whatever. But the body is elongated so as to remind us of an ascidian, having its ganglion and the part of the body-wall containing it so much extended as to remove the anal considerably from the oral aperture. The muscles of this elongated body require innervation, and thus the ganglionic mass is elongated into a cord called the myelon, which represents the spinal cord as well as the medulla oblongata. In ascidians then we have a mass corresponding to the medulla; in the amphioxus we have a mass corresponding to medulla and spinal cord.

In a fish the pharyngeal or branchial sac, instead of opening into the atrial sac, opens directly into the surrounding water.

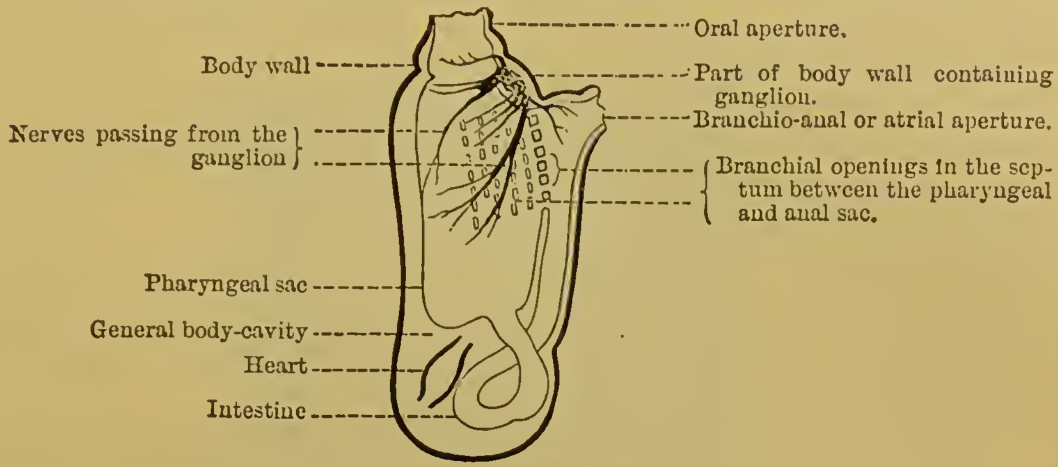

FIG. 77.—Diagram of an Ascidian.

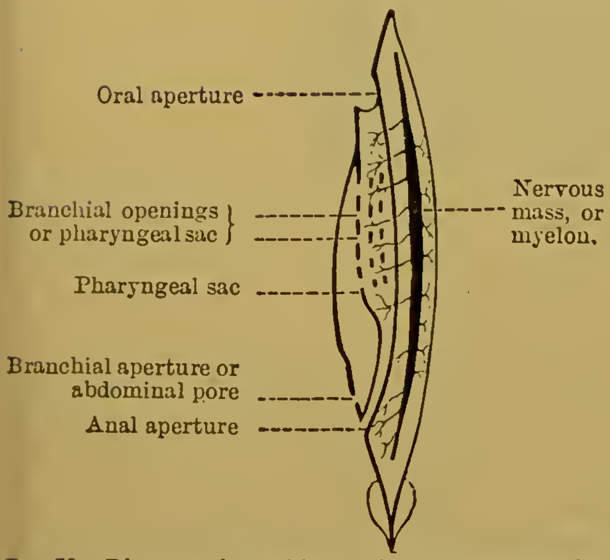

FIG. 78.—Diagram of Amphioxus. The water enters the oral aperture, passes through the openings in the pharyngeal sac into another cavity, whence it escapes by the abdominal pore.

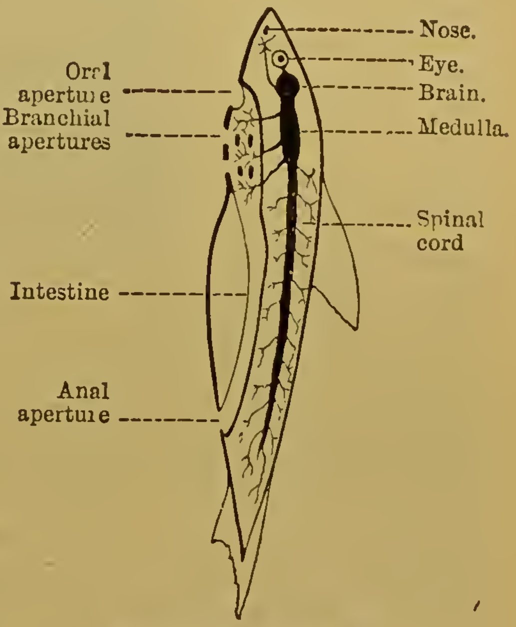

FIG. 79.—Diagram of fish.

We have a head and organs of special sense, and therefore we have a large nervous mass or brain.

In these three members of the animal kingdom, therefore, we have the medulla as the lowest or fundamental centre, next the spinal cord, and lastly the brain. We might therefore expect that notwithstanding the apparently higher position and greater nearness of the medulla to the brain than to the spinal cord, the medulla would be less readily affected by many drugs than the cord or the brain, and this is what we find in the case of such drugs as alcohol, ether, or morphine, which appear to paralyse the nervous centres in the inverse order of their development—the brain first, spinal cord next, and medulla last.

There are some drugs, however, e.g. aconite, gelsemium, and

hydrocyanic acid, which seem to have a special paralysing action on the respiratory centre.

If we look at the ganglionic mass in an ascidian, represented in the diagram, we shall see that it sends some fibres to the pharyngeal sac and some to the anal sac. If these two sacs were to contract together they would oppose each other's action, and thus the passage of water through the branchial apertures would be stopped, and respiration consequently arrested. They must therefore act alternately, and this alternate action is regulated by the ganglion. This ganglion consists of numerous nerve-cells and fibres. As some of these have a more special connection with the pharynx, the group which they form may be called the pharyngeal centre or inspiratory centre.

Similar arrangements occur in higher animals, and the terms used in regard to their nervous system may lead to some confusion of thought; thus we speak of the respiratory, of the inspiratory, of the expiratory, and of the vomiting centres.

By **nerve-centres** we simply mean the **groups** of **cells** and fibres which are concerned in the **performance** of certain **acts.** They are not necessarily entirely distinct from one another, and the same group of ganglionic cells may form a part of several centres. Thus in the accompanying diagram (Fig. 80), the **respiratory** centre includes both **inspiratory** and **expiratory** centres, and the vomiting centre includes some ganglionic groups which form part of the inspiratory, and others forming part of the expiratory centres, besides other ganglion groups which are concerned with the simultaneous dilatation of the cardiac orifice of the stomach. On analysing this subject still further we find also that the inspiratory centre affects many muscles, and that it does not always affect them to the same extent. Thus in men the diaphragm takes a more active share in inspiration during the day than the thoracic muscles. During sleep the diaphragm takes a much less active part, and may be entirely quiet, while the thoracic muscles are more active, and the chest rises and falls more than during walking.

The **inspiratory** centre might be thus still further divided into **thoracic** inspiratory centre, and **diaphragmatic** inspiratory centre.

Such subdivisions appear absurd if we imagine that each centre represents a distinct nervous mass, and we become puzzled to understand how the medulla oblongata can contain so many distinct centres in a small bulk. But if we remember that the word '**centre**' simply indicates a group of cells and fibres connected with the performance of a particular act, and that two centres may be formed by the same ganglionic groups and differ from one another only by having a few ganglion cells more or less which alter the function they perform, no harm is done by the use of the term.

The act of **respiration** consists in the alternate enlargement and diminution of the thoracic cavity, so that the air is alternately inspired and expired.

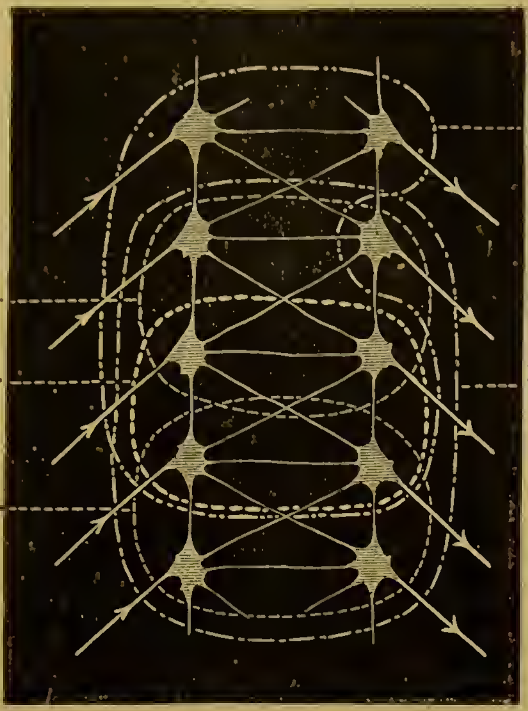

FIG. 80.—Diagrammatic representation of various groups of ganglion cells, or 'centres,' in the medulla oblongata. The arrows indicate the directions in which the nerve-currents pass. Those pointing to the cells indicate sensory, those pointing from the cells indicate motor, nerves.

The **muscles** by which this is effected in ordinary respiration are the diaphragm and intercostal and scaleni muscles. The diaphragm descends, and the intercostal and scaleni muscles raise the ribs during **inspiration.**

Expiration is normally a **passive** act,[1] and is not performed by muscular action, but simply by the tendency of the diaphragm and thoracic walls to return to the position of the equilibrium from which they had been removed during inspiration, and by the contraction of the elastic walls of the air-vesicles distended by inspiration.

When the supply of oxygen is deficient, other muscles are called in to aid the inspiration. Expiration appears to be a passive act, not merely in ordinary respiration, but even in dyspnœa caused by the absence of oxygen. In some experiments by Bernstein[2] the inspiration and expiration were equally increased in a rabbit, when the air which it had breathed was replaced by hydrogen. But expiratory efforts are required both for the production of voice, and for the removal of irritants from the air-passages by coughing or sneezing; and forcible expira-

[1] Bernstein, *Archiv f. Anat. u. Physiol.*, 1882, p. 322.
[2] *Ibid.*, *op. cit.*

tion is produced when an irritant is applied to the mucous membrane of the nose, of the larynx, trachea, or bronchi. As every one who has drunk a bottle of soda-water knows, carbonic acid is an irritant of considerable power to these mucous membranes, and when it is breathed instead of air or hydrogen the expiration becomes much more powerful, and is no longer a passive action, but an active one, performed by active muscular exertion.

The chief **respiratory centre** is situated in the medulla oblongata close to the end of the calamus scriptorius, at the point designated *nœud vital* by Flourens, because destruction of this point arrests the respiration and causes death.

It extends equally on both sides of the middle line in the medulla, each half regulating the breathing on the same side of the body. It has been supposed to be double, and to consist of inspiratory and expiratory centres which act alternately, but it would appear that in ordinary respiration the inspiratory centre only is active.

When the centre is injured by a puncture, as in Flourens' experiment, or when one half of it is destroyed, breathing usually stops entirely, but if the respiration be kept up artificially for several hours, the normal breathing again becomes established; and the prolonged continuance of artificial respiration has been recommended by Schiff in apoplexy.

When the connection between this centre and the respiratory muscles is cut off by dividing the spinal cord just below the medulla, respiration usually ceases entirely, so that at first sight it would seem that the respiratory centre is limited to the medulla.

The effects of strychnine show that this is not the case. This drug greatly increases the excitability of the respiratory centre, and when it is injected into the blood before division of the spinal cord, the respiratory movements still continue to some extent after the cord has been divided. When it is injected after section of the cord, the respiratory movements which had ceased again recommence to a slight degree.

The reason appears to be that the **respiratory centre** is not limited to the **medulla**, but extends to the upper part of the **spinal cord**, though the spinal portion is of itself too weak to keep up the respiratory movements, except when stimulated by strychnine.

The **amount of respiratory work** which this centre excites appears to **depend** to a great extent, though not entirely, upon the condition of the **centre** itself.

The **distribution** of the work is chiefly determined by the irritation of one or other of the afferent **nerves**, and these nerves also influence the amount of work.

The **centre** is stimulated, and the amount of work it does increased by a venous condition of the blood circulating in it.

An arterial condition of its blood lessens or completely abolishes its activity, so that when the blood is highly aërated by forced artificial respiration, a condition of **apnœa** is produced, in which no spontaneous respiratory movements occur.

This condition is much more readily induced when the excitability of the respiratory centre is lessened by drugs. In an animal poisoned by chloral, for example, it is very easy to induce it, and it lasts for a long time.

When the respiratory centre is excited, as by the injection of emetine or apomorphine into the circulation, it is difficult or impossible to produce this condition.

It is uncertain whether the stimulation which the venosity of the blood produces is due chiefly to the absence of oxygen or to the presence of carbonic acid. Possibly it may also be due to the products of imperfect combustion in the venous blood. Or all these three causes may share in the stimulation, though to what extent each does so is not known.

According to Bernstein, want of oxygen appears to stimulate the inspiratory and the presence of carbonic acid to stimulate the expiratory centre.[1]

As the blood becomes venous the activity of the respiratory centre increases, the respirations becoming quicker and deeper, and the accessory respiratory muscles are thrown into action. This condition is called **dyspnœa**. Finally the excitement extends to all the muscles of the body and we get general **convulsions**, which have usually an opisthotonic character. The eyeballs very often protrude during these convulsions, and the blood-pressure rises greatly from stimulation of sympathetic and vaso-motor centres in the medulla.

After the convulsions cease, the animal usually lies motionless, and the heart as a rule continues to beat for a short time after the respirations have ceased.

The excessive venosity of the blood in this condition has paralysed the nerve-centres, but if artificial respiration be now commenced and the blood becomes gradually aërated, the conditions just described are again passed through in the reverse order: convulsions first reappearing, then dyspnœa, next normal breathing, and, if the respiration be pushed far enough, apnœa.

Asphyxial convulsions only occur in warm-blooded animals, and not in frogs, and when we find that any drug produces convulsions in mammals and not in frogs we usually assume that the convulsions are due to asphyxia produced by the action of the drug on the respiration or circulation, and not to a direct irritant action upon the motor centres. If, on the other hand, we find that the convulsions occur in frogs as well as in mammals, the presumption is in favour of their being due to the direct irritant action of the drug on motor centres.

[1] Bernstein. *op. cit.* p. 324.

Blood becomes venous when the external respiration or interchange of gases between it and the external air is arrested while internal respiration continues.

Internal respiration or interchange of gases occurs between the blood and the tissues outside the vessels which are consuming oxygen and deriving it from the blood. But the blood although fluid is itself a tissue and likewise consumes oxygen, so that it will become venous if left to itself in a thoroughly-stoppered glass bottle.

External respiration may be arrested or diminished by—

(1) Interfering with the access of air to the blood; or
(2) ,, ,, ,, ,, ,, blood to the air; or
(3) ,, ,, ,, power of the blood to take up and give off oxygen.

The access of air to the blood may be prevented by obstruction to the air-passages or alteration in the structure of the lung; thus anæsthetics may obstruct respiration by allowing vomited matters to enter the trachea and plug it mechanically. Apomorphine may lead to obstruction of the bronchi by profuse secretion from the mucous membrane, and large doses of antimony may cause consolidation of the lung.

Air may be prevented from reaching the blood by any obstruction in the respiratory passages.

The respiratory passages may be obstructed by spasmodic closure of the glottis or of the nostrils in rabbits when an irritating vapour is inspired. This source of obstruction is easily avoided by putting a cannula into the trachea and allowing the vapour to be inspired through it. Another source of obstruction is the formation of plugs of mucus or clots of blood in the trachea or in the cannula, which has been introduced into it. Occasionally a plug of mucus, and sometimes a clot of blood, forms in the tracheal cannula and seriously impedes the respiration, whether natural or artificial, without being perceived by the experimenter. In order to be sure that such an occurrence has not taken place and vitiated the results, it is always advisable, on removing the cannula from the trachea at the end of an experiment, to blow through it and see that its lumen is perfectly unobstructed.

Access of air to the blood may be prevented also by paralysis of the muscles of respiration; thus curare will produce it by paralysing the ends of the motor nerves, hydrocyanic acid by paralysing the respiratory centre, and snake poison by paralysing both.

The blood may be prevented from reaching the lungs by arrest of the circulation either local or general, and may thus become venous, either locally or generally.

The **venosity** of the blood circulating in the medulla may be altered **locally** without any change in the rest of the body. Thus if the carotid and vertebral arteries are tied, the blood stagnates in the vessels of the medulla, and there becoming venous causes dyspnœa and convulsions, which again disappear when the ligatures are loosened and the circulation re-established.

Dyspnœa and convulsions are likewise produced by alteration in the **general** circulation, e.g. by loss of blood, as is seen when an animal is bled to death, or when the supply of blood in the arteries is greatly diminished by ligature of the portal vein, which causes the blood to accumulate and stagnate in the capacious veins of the intestine.

Stoppage of the **heart**, either by ligature directly applied to it or by the action of drugs upon it, causes asphyxia and convulsions.

Arrested circulation through the **pulmonary** vessels by emboli has a similar action. This sometimes leads to error in regard to the action of drugs when these are injected, as is often done, into the jugular vein.

If they contain solid particles, these may give rise to embolism in the pulmonary arteries and lead to the belief that the drug has a tetanising action, when, as a matter of fact, it has nothing of the kind. Thus, in making an experiment on condurango, I injected an infusion into the jugular vein of a rabbit, and it rapidly died with symptoms resembling those of strychnine-poisoning. The cause of this, however, was simply embolism of the pulmonary vessels, due to undissolved particles in the infusion, and when this was avoided by injecting the drug into the peritoneal cavity, no symptom whatever was produced. Gianuzzi, in his experiments on this drug, appears to have fallen into the same error as I did at first.

Altered condition of the **blood** also gives rise to dyspnœa, as is seen in the breathlessness of anæmia, where the blood is unable to take up the quantity of oxygen necessary for any exertion, and the patient pants violently after any quick movement, such as going up stairs.

Dyspnœa and even convulsions are also caused by nitrites, e.g. nitrite of amyl or sodium, which lessen the power of the blood to give off oxygen, and by carbonic oxide, which replaces the oxygen in the blood.

It must be remembered, however, that, whatever may be the remote cause of dyspnœa, its direct cause is the condition of the nerve-cells in the medulla, and if these are unable to take up oxygen, and give off carbonic acid to the blood, dyspnœa may occur, although the blood itself circulating in the medulla contains abundance of oxygen.

In the case of carbonic-oxide poisoning the blood cannot take up oxygen from the lungs, although there is abundance of oxygen present; and in a similar way the nerve-cells of the medulla may possibly be rendered by certain drugs unable to take up oxygen from the blood circulating through the medulla.

In simple suffocation the **internal respiration** of the nerve-cells in the medulla is arrested by the general venous condition of the blood; in carbonic-oxide poisoning by the oxygen being absent

from the hæmoglobin; in nitrite poisoning by the oxygen being locked up in methæmoglobin. In all those cases the condition of the blood is betrayed to the eye by the appearance of the mucous membranes, which in suffocation and in nitrite poisoning become dark and livid, and in carbonic-oxide poisoning of a cherry-red colour. Perhaps the change is most conveniently seen in the comb of a cock poisoned by these substances; in it the alteration in the colour of the blood produced by artificial respiration is readily observed. The dependence of convulsions upon the blood is also easily observed: the convulsions appearing as the comb becomes livid, and again disappearing when artificial respiration has been employed, and the colour of the comb becomes bright. In poisoning by hydrocyanic acid, however, I have observed that convulsions come on while the mucous membranes are still of a bright colour, so that we may conclude that they are not due to a venous condition of the blood, as in ordinary suffocation. They might be due to the formation of a compound between the hydrocyanic acid and the blood, as in poisoning by nitrites or carbonic oxide; but accurate analyses have shown that hydrocyanic acid does not displace the oxygen in hæmoglobin like carbonic acid, nor lock it up in the form of methæmoglobin like the nitrites. We are therefore obliged to consider the possibility that the dyspnœa and convulsions produced by hydrocyanic acid are not due so much to its effect upon the blood circulating in the medulla as to an action on the cells of the medulla itself, by which it prevents the ordinary internal respiration taking place in them.

Action of Drugs on the Respiratory Centre.

A useful method of testing the action of the drug itself on the respiratory centre is to perform artificial respiration vigorously so as to produce apnœa, to allow the respiration to become normal again, then to inject the drug and again try to produce apnœa. If the drug has excited the respiratory centre, apnœa will be much more difficult to produce after its injection than before, and will last a shorter time; if it has depressed it, apnœa will be more easily produced, and will last longer.

Apnœa lasting for a short time may be readily produced by taking five or six very deep breaths, and the effect of drugs on the respiratory centre may be readily tried by anyone in the following way. Laying a watch before him, shutting his mouth and holding his nose, let him first ascertain how many seconds he can hold his breath after previous ordinary respiration. Next let him produce a certain amount of apnœa by six or more deep respirations, and again ascertain how long he can hold his breath. After repeating these observations several times, let him take the drug to be tested and repeat them again, taking care that all the circumstances should be the same as before.

The **activity** of the **respiratory centre** is augmented by heat, so that the respirations become both quicker and deeper, and more respiratory work is done. Strychnine, ammonia, atropine, duboisine, brucine, thebaine, apomorphine, emetine,

members of the digitalis group, salts of zinc and copper, have a similar action.

It appears to be first excited and then depressed by caffeine, colchicin, nicotine, quinine, and saponine.

It is diminished by cold, so that the respirations become slow and shallow. Chloral, chloroform, ether, alcohol, opium, physostigmine, muscarine, gelsemine, aconite, and veratrine in large doses, all have a similar action.

The action of drugs on the respiratory centre is one of great importance, not only as giving us a definite basis on which to found a plan of treatment in respiratory diseases, but as helping us to preserve life in cases of poisoning—drugs which stimulate being antagonised by those which depress the respiratory centre, and *vice versâ.*

The chief **afferent nerves**, by which the distribution of the respiratory movements is altered, may be divided into two classes —those having an inspiratory and those having an expiratory action.

The **expiratory** are the nasal branches of the fifth, the superior laryngeal, the inferior laryngeal, and the cutaneous nerves, especially of the breast and belly.

The chief **inspiratory** are the branches of the vagus going to the lung, but all sensory nerves when slightly stimulated appear also to have an inspiratory action.

The vagus appears, however, to contain both expiratory and inspiratory fibres, which are alternately stimulated by the condition of the lung. Expansion of the lung appears to stimulate mechanically the inhibitory or expiratory fibres; while its collapse stimulates the accelerating or inspiratory fibres.

When the **expiratory** nerves are stimulated, the respiratory movements become **slower** and deeper; and if the stimulation be strong they may stop altogether in expiration, with the diaphragm in complete relaxation.

Stimulation of the **inspiratory** nerves causes the respiration to become **quicker** and shallower, and at length to stop in inspiration, the diaphragm being in a state of tetanic contraction.

These are the general **results**, but they are **not** quite **constant.** The reason for this inconstancy may be either that all the nerves contain both inspiratory and expiratory fibres, or that the same fibres may stimulate either the inspiratory or expiratory centres, according to the strength of the stimulus and the condition of the animal. Thus, when the vagus is divided, the stimulus which is conveyed to the respiratory centre being removed, the respirations usually become very slow; when the central end of the divided nerve is irritated they become quick, and a very strong current may stop them in inspiration. But this is not always so: when the nerve is very much exhausted, irritation by a strong current may have an entirely **opposite** effect,

and cause the respiration to stop in expiration instead of inspiration.

The probability that the same nervous fibres may, under different conditions, excite either inspiration, expiration, or the two alternately, is rendered still greater when we consider some other experiments; and the contradictory results which have been obtained by various observers in regard to the action of drugs may depend to a great extent on the strength of the stimulus they have used and the state of exhaustion of the animal. Thus Langendorf has found that all sensory nerves in the body when slightly stimulated have an inspiratory, but when stimulated more strongly have an expiratory action. Rosenthal found that irritation of the crural nerves caused alternately deep inspiration and expiration in animals which were not narcotised. In narcotised animals, Langendorf, on slight irritation, observed an inspiratory effect, indicated by quickening of the respiration or slight inspiratory tetanus; but when the experiment was continued long, or the irritation was increased, the contrary or expiratory effect was observed, indicated by a slowing of the respiration.

On the hypothesis that the various actions of respiration depend upon individual centres, inspiratory, expiratory, and in-

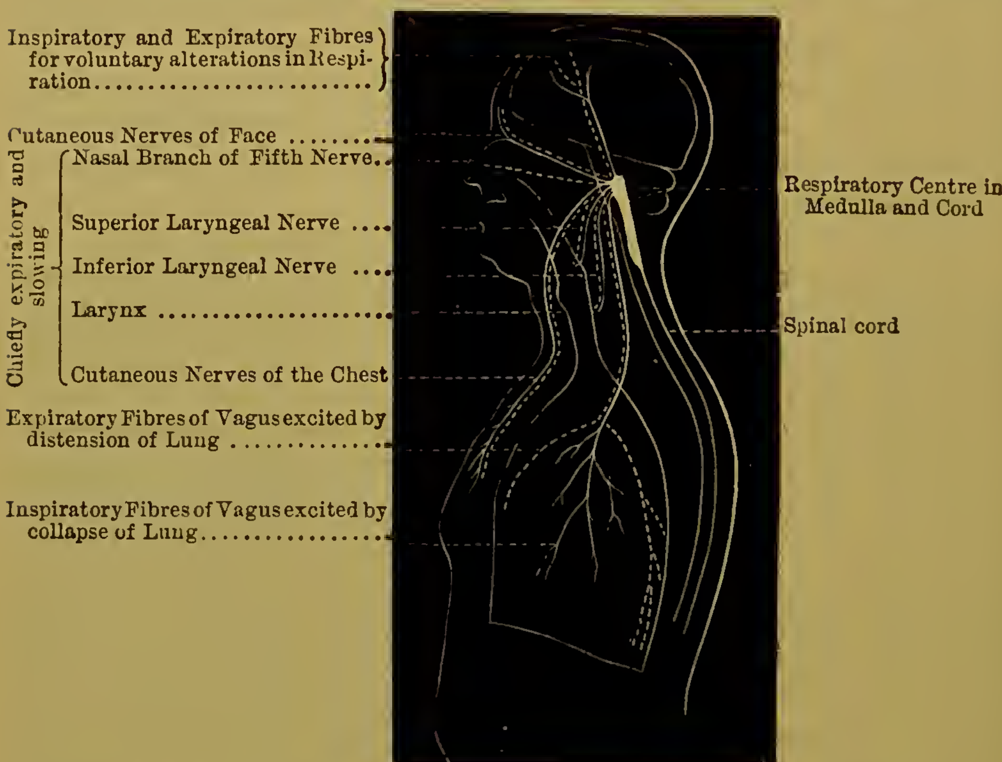

FIG. 81.—Diagram showing the position of the respiratory centre, and the afferent nerves which influence it. Inspiratory nerves are indicated by plain, and expiratory by dotted, lines.

hibitory, it is exceedingly difficult, or impossible, to understand the contradictory results of various experimenters; but the question seems much less intricate when we regard it as due to the

interference of stimuli passing at different rates in different directions, or to different distances, according to the strength of the stimulus and the irritability or exhaustion of the nervous system.

In regard then to inhibitory or slowing, and to stimulating or accelerating nerves or fibres, it must be carefully borne in mind that the same fibres may possibly have either the one or the other action, according to the conditions under which they are acting.

If we keep this carefully in view we may continue to use the terms accelerating and slowing or inspiratory and expiratory nerves as convenient means of expression. These are shown in the accompanying diagram (Fig. 81).

The movements of respiration are most easily counted, and their depth and the relation of inspiration to expiration are best noted by causing them to register themselves on a revolving cylinder. Various means of doing this have been suggested by different authors. One of the simplest consists of a needle pushed into the diaphragm, and connected by a thread with one of Marey's levers. Marey's pneumograph consists of a cylinder of soft indiarubber, enclosing a spiral spring, whose extremities are connected with two pieces of metal which form the ends of the cylinder. A band is passed round the thorax of the animal, and attached to the ends of the cylinder. The interior of the cylinder is brought into communication with one of Marey's levers, and as each respiratory movement draws the ends of the cylinders wider apart, or allows them to approach, the air is rarefied or compressed, and a corresponding movement is transmitted to the lever. Bert has modified this, and made it more sensitive by making the cylinder itself of metal, and its ends of indiarubber. Another method—one more ordinarily employed—is to introduce one limb of a T-tube into the nostril or trachea of an animal, or connect it with a tracheal cannula. The respired air passes through the other end, and the third limb is connected with one of Marey's levers.

In the attempt to find out whether the alteration in respiration produced by any drug is due to its action on the respiratory centre, or on some of the nerves which influence it, we may find the following table useful by showing at a glance the chief ways in which the respirations may be rendered **quicker** or **slower**:—

The respiratory movements may be **quickened** by	Excitement of nerves.	Stimulation of the vagus. Stimulation of optic nerve. Stimulation of acoustic nerve.
	Greater excitement of respiratory centre.	Action of brain (voluntary). Increased temperature of blood. Increased venosity of blood. Action of drugs.
The respiratory movements may be rendered **slow** by	Diminished excitement of respiratory centre.	Diminished venosity of blood. Action of drugs. Action of brain (voluntary).
	Nervous influences.	Paralysis of vagi. Stimulation of superior laryngeal nerves. Stimulation of inferior laryngeal nerves. Stimulation of nasal nerves. Stimulation of cutaneous nerves. Stimulation of splanchnic nerves.

If the drug to be experimented on be injected subcutaneously or into the veins, the actions on the respiratory centre and on the vagi are the chief points which require attention; but if we are experimenting with a vapour, its local action on the nasal, laryngeal, and possibly, also, on the pharyngeal nerves [1] must be carefully attended to, as it may greatly modify its general action on the respiratory centres. Thus Kratschmer has found that tobacco-smoke inhaled by a rabbit through its nostrils, or blown upward into the nasal cavity from an aperture in the trachea, will cause arrest of breathing in a state of expiration from the irritating effect of the vapour of the nasal branches of the fifth, while it has no such effect when blown into the lungs. Ammonia, when inhaled, also arrests the respiratory movements in the same way; but Knoll [2] has observed that if it be blown into the lungs while the nostrils are carefully protected from its influence, it causes accelerated and shallow breathing, alternating with slow and deep respirations, and occasional stoppages in the position of expiration, obviously from its action on the different fibres of the vagi.

Action of Drugs on the Respiratory Nerves.

In experiments regarding the effect of drugs upon the respiration, the voluntary influence of the brain is excluded by the use of ether, chloroform, opium, or chloral, or by section of the crura cerebri. In the case of such poisons as cause sickness allowance must be made for the effect of gastric irritation. It will usually be found that before vomiting occurs the respiratory movements are very rapid, but they become slower after vomiting has taken place. As the chief afferent fibres from the stomach are contained in the vagus, the effect of irritation of the gastric, as well as of other fibres contained in these nerves, is prevented by their division. Sometimes the action of a drug on the peripheral ends of the vagus and upon its roots in the medulla may produce exactly opposite effects upon the respiration. Thus atropine appears to lessen the excitability of the respiratory fibres of the vagus, while it stimulates the respiratory centre. Such an action may be to a certain extent inferred from the respiration becoming slower almost immediately after the injection of the drug into the jugular vein, and while it is still passing through the lungs, and by this slowing being quickly succeeded by acceleration when the drug begins to circulate through the medulla.

There are two kinds of experiment by which such a conclusion may be tested. The one is to apply the drug first to the

[1] Brown-Séquard, *Archives of Scientific and Practical Medicine*, p. 94.
[2] *Sitzungsber. der Wien. Acad.*, vol. lxviii. Abt. 3, p. 255.

medulla by injecting it into the carotid artery, and seeing whether acceleration occurs at once and afterwards becomes less when the drug has had time to pass round again to the lungs. The other way is to divide the vagi before the injection and observe the effect. Any alteration in the respiration in the way of either quickening or slowing which the drug produced in the uninjured animal should remain the same after division of the vagi if its effect were due to its action on the medulla, but will be absent if it were due to an action upon the peripheral ends of the vagi.

This method was introduced into pharmacological research by Von Bezold in his admirable research on atropine, and it is the one usually employed.

There is one fallacy, however, which must not be entirely lost sight of, which is, that after division of the vagi the nerves which remain in connection with the respiratory centre have chiefly a slowing action on the respiration; and thus a drug which really renders the respiratory centre more susceptible to reflex influences might seem to have a depressing action upon it.

While atropine injected into the jugular vein seems to produce first a slowing of the respiration, due to its paralysing action on the vagus ends, and afterwards a progressive quickening as more of it is carried out of the lungs into the medulla, physostigmine, muscarine, and veratrine have an opposite action, quickening the respiration at first by their stimulating action on the vagus ends, and afterwards slowing it by their action on the medulla.

In the action of veratrine upon the pulmonary branches of the vagus we may notice a resemblance to the stimulant action, which, as already mentioned, it exerts upon the nerves of ordinary sensation. If the sensory branches of the vagus are affected by drugs in a somewhat similar way to those of ordinary sensation, as the action of veratrine might lead us to imagine, we should expect them to be much stimulated also by aconite, and, indeed, according to Boehm and Ewers, this is the case. The respiratory changes produced by aconite are regarded by them as due, in part, to irritation of the peripheral ends of the vagus, and disappear on section of the vagi or the administration of atropine.

Sternutatories or Errhines.

These are drugs which cause **sneezing** and increased secretion from the nose when locally applied to it. The drugs must be in a pulverised condition. The chief are:—

Tobacco (snuff).	Euphorbium.
Veratrum album.	Sassy bark.
Ipecacuanha.	Saponine.

Irritation applied to the nose is transmitted by the nasal branches of the fifth to the **respiratory** centre in the medulla oblongata, and excites the sudden and forcible expiratory movements of sneezing. At the same time, however, the stimulus is transmitted to the vaso-motor centre, and the **blood-pressure** becomes considerably increased by the contraction of small vessels throughout the body, even when no sneezing occurs. When sneezing takes place, the pressure is still further increased by the muscular efforts which occur in the act. It is probable that there is not only general rise in blood-pressure but also that local dilatation of the **cerebral** vessels is reflexly produced by the nasal irritation, and thus a **stimulant** effect is produced on the brain. Snuff is therefore employed as a luxury giving a feeling of comfort and enabling the snuff-taker to think more clearly—'clearing the head' as it is often termed (*vide* p. 193).

Uses.—Though comparatively little used now, sternutatories were formerly employed in failure of memory, deafness, and severe persistent headache. From the violent expulsive efforts which they induce, they were given also to cause the expulsion of foreign bodies from the air-passages, and to hasten the expulsion of the child in cases of lingering labour where no obstruction was present, but where expulsive force was deficient. They were given also in order to try and check diseases at the commencement, by what was termed 'shock to the system.'

One curious thing is to be remarked, that stimulation of one part of the respiratory tract may arrest abnormal actions in another. Thus Marshall Hall has shown that actual sneezing may frequently be prevented, after the inspiration by which it is usually preceded has occurred, by forcibly rubbing the end of the nose or by tightly compressing the nostrils. In a similar way irritation of the interior of the nose by snuff will sometimes arrest obstinate hiccough.

Contraindications.—On account of the high blood-pressure which they produce their use is by no means free from danger in persons affected with atheroma or a tendency to pulmonary hæmorrhage or apoplexy, as they may cause rupture of a vessel, and in those who suffer from hernia or from prolapsus of the uterus, they may seriously increase the gravity of these affections.

Respiratory Sedatives.

These are substances which diminish **cough** and spasmodic difficulty of breathing.

They may be divided into drugs which—

(1) Tend to **remove** the **irritation** which acts as the exciting cause of the cough.

(2) Tend to lessen irritability of { (*a*) the **afferent nerves** in the lungs; (*b*) the **respiratory centre**.

Pathology of cough.—Cough consists in a deep inspiration followed by a forcible expiration with closed glottis, so that the air is driven rapidly through the larynx, carrying with it foreign substances, liquid or solid, which may be present in the air-passages. As it is a modified respiratory act, the nerve-centre by which the muscles employed in it are co-ordinated is situated in the medulla oblongata.

The afferent fibres by which cough may be excited are chiefly branches of the vagus. One of the most powerful is the superior

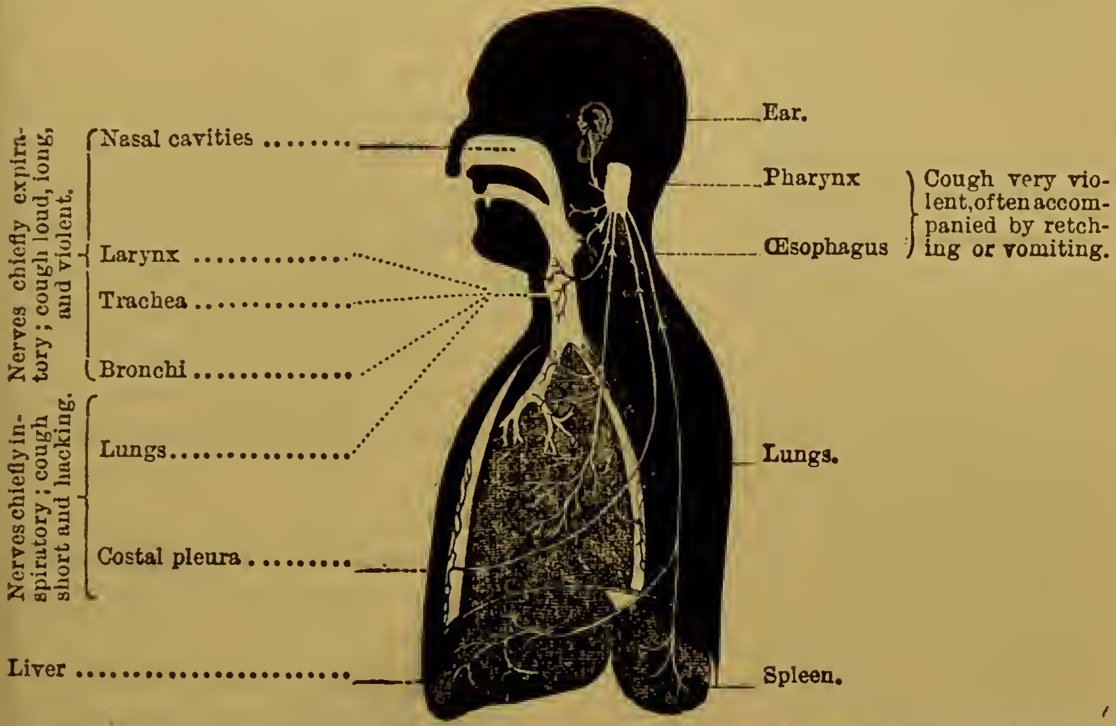

FIG. 82.—Diagram of the afferent nerves by which cough may be excited. These nerves are shown passing to the respiratory centre in the following order from above downward—from the auditory meatus, pharynx, upper part of œsophagus, larynx and trachea, bronchi, lung, costal pleura, liver and spleen.

laryngeal nerve distributed to the glosso-epiglottidean folds and to the whole of the interior of the larynx, and this being a special expiratory nerve we find that irritation of the larynx and also of the trachea is usually characterised by a cough with very violent expulsive efforts. Irritation of the mucous membrane of the trachea especially at the bifurcation of the bronchi, and irritation of the substance of the lung, also give rise to cough; and irritation of the costal pleura and of the œsophagus does so also.[1] Irritation of the auditory meatus at the point to which the auricular branch of the vagus is distributed will also cause coughing; and cough appears to be also induced by irritation of certain parts of the interior of the nose. These are the surfaces of the inferior and middle turbinated bones, the most sensitive

[1] Kohts, *Virchow's Archiv*, 66, 191.

part being the posterior end of the inferior turbinated bone and the portion of the septum immediately opposite.[1] The sudden application of cold to the skin on various parts of the body will sometimes cause coughing. Probably the cough in this case is not due to the stimulus being conveyed directly to the respiratory centre by the cutaneous nerves, but to its causing congestion of the air-passages, as in Rossbach's experiments (p. 252). The congestion then causes irritation of the sensory nerves of the bronchi, and occasions cough.

I have seen irritation of the liver and spleen, induced by percussion over them, in a man suffering from chronic enlargement due to malaria, likewise cause coughing.[2] In addition to those nerves, however, it appears that irritation of the glosso-pharyngeal branches distributed to the **pharynx**, where the digestive and respiratory tracts coincide as they cross one another, may not only excite coughing, but may also act as an auxiliary to irritation of the branches of the vagus. The combined action of the two may thus induce cough, when irritation of the vagus alone would not do so. Thus we find that many persons begin to cough as soon as they lie down, but that sometimes by lying round partially on the face, the cough ceases. In these persons the uvula is often found to be long and much congested, and the tickling which it produces as it rests upon the pharynx or pillars of the fauces seems to aid the irritation in the respiratory passages, and produce cough.

Cough due to irritation of those parts of the respiratory tract where the nerves are chiefly expiratory, as the pharynx, larynx, trachea, and large bronchi, is usually, as might be expected, loud, explosive, and prolonged; while cough due to irritation of those parts where the nerves are chiefly inspiratory is short and hacking (Fig. 82).

Cough produced by irritation of the pharynx where the respiratory and digestive passages cross one another, is not only violent, noisy, and barking, but, as we would naturally expect, is not unfrequently accompanied by retching or vomiting.

Pharyngeal irritation may accompany dyspepsia, and it is probably the origin of the so-called **stomach-cough.** Irritation of the stomach itself, or of its nerves, causes vomiting, but does not produce cough.

Nevertheless there is a *rationale* for the common expression 'stomach-cough.' In some experiments on the reflex origin of cough, R. Meyer[3] has noticed that when some part, from which

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[1] *On Nasal Cough*, by John N. Mackenzie, M.D., reprint from *The American Journal of the Medical Sciences*, July 1883.

[2] These observations were made in January and April 1879, but not published. Naunyn, in a paper published in the *Deutsch. Archiv f. klin. Med.* in March 1879 recorded similar observations.

[3] R. Meyer, *Correspondenzblatt d. Schweizer Aerzte*, No. 1, 1876.

cough can be reflexly induced, is already in a state of irritation, cough can be brought on with great ease by irritation of a neighbouring part which would not by itself cause cough. Something of this kind appears to occur with the stomach, for although irritation of the stomach alone will not cause coughing, yet it will do so if irritation of the larynx and trachea are already present. Thus I have observed violent spasms of coughing occur, along with acidity and heartburn, some time after a meal, in a person suffering from congestion of the pharynx, larynx, or trachea. The connection between the cough and the acidity was shown by the cough ceasing as soon as the acidity was relieved by a dose of alkali and the consequent removal of the irritation to the stomach, which the acidity had produced.

Remedies which Lessen Irritation.

Soothing remedies applied to the pharynx greatly relieve cough, although they do not reach so far down as the epiglottis. Mucilaginous remedies are very useful for this purpose, and they may either be employed alone or as vehicles for the local application of sedatives such as morphine. Thus, a piece of extract of liquorice allowed to dissolve in the mouth, a marsh-mallow lozenge, a gum-jujube, or a sip of linseed-tea, by covering the back of the throat with a mucilaginous coating, will lessen cough to a great extent. Such remedies are especially useful where the cough depends on congestion of the pharynx and trachea. In such cases no abnormal sound at all may be heard in auscultation, and the cough being due to irritation of the parts supplied by the superior laryngeal nerve, has a peculiarly convulsive expiratory character often termed 'barking.'

Other remedies lessen cough by **diminishing congestion** of the respiratory passages, and thus lessening the irritation which causes the cough. Many of these also, however, come under the class of **expectorants** (p. 250), inasmuch as the diminished congestion is frequently associated with increase of the expectoration. Others, again, although they diminish cough, are included rather under the head of '**cardiac tonics**,' or sedatives. Digitalis is an example of this. In the congestion due to cardiac disease, and even in that due to bronchitis, digitalis, by strengthening the heart and by contracting the vessels, may lessen the congestion in the lungs, and give the patient relief. Squill and a number of other drugs have an action on the blood-vessels similar to that of digitalis.

Other remedies, such as the vapour of hydrocyanic acid, conium, stramonium, and tobacco, have a **local sedative** action on the lung, and may lessen cough; they also are used in order to diminish local spasm of the bronchioles, and thus to relieve spasmodic asthma.

Pulmonary Sedatives.

These are remedies which lessen the irritability of the respiratory centre or of the nerves connected with it. The chief drugs which diminish the excitability of the **respiratory centre** are opium and its principal alkaloid, morphine. Morphine and opium have a double action in lessening cough: they not only **lessen** the excitability of the respiratory centre, but they diminish the secretion of mucus in the bronchial tubes, and probably thus also lessen the irritation. Hydrocyanic acid has also a sedative action on it, but it is by no means so powerful as the others.

Belladonna and stramonium have a rather peculiar action, stimulating the respiratory centre, and at the same time appearing to lessen the excitability of the ends of the vagi in the lungs. Atropine has but a very slight and uncertain action on the respiratory centre in preventing cough, if indeed it has any at all. It has, however, a powerful effect—much more powerful than that of opium,—in completely **arresting** the **secretion** from the bronchial tubes. The cases in which it is useful are therefore those where the cough depends upon excessive secretion. In cases where the mucous membrane is already too dry, it would be injurious rather than beneficial.

When apomorphine and morphine are given together they do not destroy each other's action, so that from the combination we get increased secretion from the mucous membrane, with diminished irritability of the respiratory centre, and consequently lessened cough. The cases in which this combination, then, is useful, are those where there is difficulty of breathing, continual cough, and thick tenacious mucus. When morphine and atropine are given together, also, they do not destroy each other's action; and thus dryness of the mucous membrane is produced, along with diminished irritability of the centre for coughing. This combination is therefore useful in cases of catarrh, emphysema, and phthisis, where there is copious secretion of mucus. In phthisis it is especially indicated on account of the beneficial action of atropine in also lessening sweating. Where the copious expectoration depends upon the presence of a cavity, and not on excessive secretion from the bronchi, it will not be much affected by the use of these remedies.

Expectorants.

Expectorants are remedies which facilitate the **removal** of **secretions** from the **air-passages**. The secretion may be rendered more easy of removal, either by an alteration in its character rendering it less adhesive and more easily detached

from the air-passages, or by increased activity of the expulsive mechanism.

Our knowledge of the use of expectorants is founded chiefly on empiricism. We are almost entirely indebted to the recent experiments of Rossbach for any precise information as to their mode of action.[1]

The secretion from the air-passages, like other secretions, depends partly upon the condition of the circulation, and partly on the secreting cells themselves.

In healthy conditions the increased secretion and increased circulation of blood in the mucous membrane go together, but just as in the case of the sweat-glands, these two factors may occur independently of each other, and secretion may take place rapidly when the circulation is diminished and the mucous membrane is anæmic, and, on the other hand, it may stop altogether when the vessels are dilated and the mucous membrane is congested. The latter happens both in cases of disease and in animals poisoned by atropine.

The **secretion** from the normal respiratory mucous membrane consists of a thin solution of mucin which dries very slowly, and is only secreted in sufficient quantity to keep the mucous membrane moist. It is slightly adhesive, and any particles of dust, &c., which may have found their way into the trachea, will stick to the walls of the air-passages, and will be gradually moved up towards the mouth by the **cilia** with which the cells of the mucous membrane are furnished. Any excess of mucus secreted in consequence of irritation will also be moved upwards by the cilia in a similar manner. In the ciliated cells of the mucous membrane we recognise a structure which is frequently met with in animals lower down the scale of existence, and the mucous membrane of the respiratory passages appears to resemble the parts of lower organisms, in being very slightly controlled by the central nervous system. When not irritated it secretes slowly and regularly; when irritated locally the secretion is increased, but irritation of the nerves passing to it, such as the vagus, the superior or inferior laryngeal, or the sympathetic, does not cause any increase as it does in the case of the submaxillary gland. These nerves, however, can influence it indirectly through the circulation, for when they are divided an increased dilatation of the vessels occurs in the mucous membrane of the trachea, a freer circulation of blood occurs, and increased secretion is thus indirectly produced. When they are irritated, however, and anæmia of the trachea produced, the secretion is not arrested, but continues.

The **circulation** in the mucous membrane is readily affected reflexly by irritation of other parts of the body. When, for

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[1] *Festschrift der Julius-Maximilian-Universität zu Würzburg*, Leipzig.

example, a warm poultice is laid for five or ten minutes on the belly of an animal, and then afterwards replaced by ice, the mucous membrane of the trachea and larynx becomes in half a minute deadly pale from the contraction of its vessels. Though the ice is still allowed to remain on the belly, the tracheal mucous membrane quickly changes colour, and to the paleness succeeds first slight redness, then deep red congestion, and in five or ten minutes lividity. This lividity shows that the congestion is not arterial but venous, and that the circulation, instead of being quicker is really slower. Along with the increase of congestion in the mucous membrane, the amount of **mucus** secreted increases. When the ice is removed for half an hour, and again replaced by the warm poultice, the bluish-red colour of the mucous membrane almost immediately disappears and gives place to a rosy colour which is, however, redder than normal. Ice again applied will cause a second contraction of the vessels and paleness, though much less than before. These experiments show how sensitive is the mucous membrane of the trachea to reflex stimulation of other parts of the body by heat or cold, and enable us to understand more readily how a draught of cold air on some part of the body should cause inflammation of the respiratory organs.

Action of Drugs on the Secretion.—**Alkalies,** such as carbonate of sodium, injected into the blood, lessen, or in large quantity completely arrest, the secretion of mucus from the trachea.

This experimental result is in contradiction to the teaching of clinical experience, which shows us that alkalies increase the amount of secretion, and render it more fluid. The results of clinical observation are quite as certain as those of Rossbach's experiments, for we may not only remark the greater quantity of expectoration, and its greater fluidity in persons taking alkalies, but we may note the alteration which they occasion in the amount and nature of the moist *râles* heard within the lungs. This can be observed most readily in persons suffering from phthisis, especially round the margin of the cavity. After catching a slight cold an extension of consolidation may be remarked, in which moist *râles* readily occur on the administration of dilute alkalies. When these are continued until the expectoration has been free for a day or two and the *râles* diminish, acids may be given with advantage, so as to dry up the expectoration still more. But if the acid is given too soon the expectoration diminishes, but the cough increases and becomes troublesome to the patient.

In all probability the difference between the results of clinical observation and Rossbach's experiments depends upon the difference of dose, the quantity usually given to a patient being proportionately much smaller than that which he employed. We

are able to observe a similar difference between the effects of small and large doses in the case of iodide of potassium; a small dose of a grain and a half, taken by a healthy man three times a day, will almost certainly cause the nose to run freely, while if the dose be increased to ten, twenty, or thirty grains the excessive secretion will almost certainly be arrested.

The local application of one to two per cent. solution of sodium carbonate has very little action. The local application of strong liquor ammoniæ causes both congestion and increased secretion of mucus. Very strong solutions cause a croupous exudation from the surface of the mucous membrane. The local application of dilute acetic acid (three per cent. solution) has a similar action to weak solutions of ammonia: the mucous membrane becoming redder and secreting more mucus.

When acetic acid was given internally, Rossbach observed in one case that the mucus, which was before watery and clear, became gelatinous and opalescent. This result agrees with what one finds clinically, that acids dry up the secretion and make it harder to expectorate.

Among **astringents** Rossbach tried tannin, alum, and nitrate of silver; the first two when locally applied made the mucous membrane appear paler by altering the epithelium and rendering it opaque, so that the vessels underneath could hardly be seen; at the same time they arrested the secretion of mucus almost entirely. A four per cent. solution of nitrate of silver also caused opacity of the epithelium, arrest of secretion, and dryness of the mucous membrane. There appears to be a difference in the action of nitrate of silver on the mucous membrane of the nose and on the trachea, as when the inside of the nose is touched by it, it causes a profuse secretion, whereas it causes dryness in the trachea.

The vapour of oil of turpentine mixed with air arrests the secretion of mucus, whilst a current of air alone, without admixture with oil of turpentine, will act as an irritant to the mucous membrane and increase secretion. Here again, however, a marked difference is to be seen in the effect of small and large doses, for when a watery solution containing from one to two per cent. of oil of turpentine was dropped directly on the mucous membrane, it became less vascular, but the secretion was at once increased, instead of being diminished, as it was by the vapour.

This action of oil of turpentine is of great therapeutical importance, inasmuch as in many cases of bronchitis we have profuse secretion with vascular congestion, a condition likely to be removed by the vapour of oil of turpentine.

Apomorphine, emetine, and pilocarpine, when given internally, all cause a great increase of the secretion of mucus, but they do not alter the vascularity of the mucous membrane. The

most powerful of all these is pilocarpine, and after it come apomorphine and emetine. One would therefore expect that pilocarpine would be the best remedy in catarrhal conditions, but this is not the case, for its other actions on the salivary and sweat glands and on the heart render its administration unpleasant for the patient. Sometimes also in children œdema of the lungs has followed its use. Apomorphine, on the contrary, has been found by Rossbach to be of the greatest service in catarrh of the larynx, trachea, and bronchi, both in adults and in children. Ipecacuanha has long been recognised as one of the most useful expectorants, but the dose given is often too small.

Rossbach's experiments have shown that the consequence of sudden changes of heat and cold applied to a part of the body is congestion of the respiratory mucous membrane with **diminished** circulation and stagnation of blood in the veins. A similar condition occurs in many cases of chronic bronchitis, and in them we not unfrequently find great benefit from **vascular tonics** such as digitalis, which, in addition to stimulating the vaso-motor centre, increase the activity of the heart, and thus tend to maintain the pulmonary circulation.

In what way cod-liver oil affects the bronchial mucous membrane it is perhaps hard to say, but there is no doubt whatever that it is one of the most efficient expectorants that we possess, and in cases of chronic bronchitis it affords more relief than any of the ordinary expectorants. It is possible that, being a form of fat which is readily assimilated, it is taken up by the young epithelial cells of the respiratory mucous membrane, and thus enables them to grow and maintain their attachment to the mucous membrane, instead of being at once shed in an undeveloped form as pus-cells in the expectoration.

Action of Drugs on the Expulsive Mechanism.—The expectorants which act by increasing the activity of the expulsive apparatus may be divided into—

(1) Those which increase the rapidity of the **ciliary motion** in the tracheal mucous membrane.

(2) Those which increase the activity of the **respiratory centre.**

We have no direct experiments or observations on the rapidity of the ciliary motion in the bronchial mucous membrane of the higher animals, but ammonia has been found to increase its rapidity in the mucous membrane of the frog.

The remedies which increase the activity of the respiratory centre are: strychnine, ammonia, emetine, ipecacuanha, belladonna, atropine, senega, and saponine. They are used more especially in cases of bronchitis where the expectoration is imperfect.

The chief expectorants have been divided into depressant and stimulant. They are as follows:—

Depressant Expectorants.

Generally tending to depress the heart, lessen blood-pressure, and increase secretion.

- Antimonial preparations.
  - Tartar emetic.
- Alkalies.
- Ipecacuanha.
  - Emetine.
- Lobelia.
  - Lobeline.
- Jaborandi.
  - Pilocarpine.
- Apomorphine.
- Quebracho.
  - Quebrachine
- Potassium iodide.

Stimulating Expectorants.

Generally stimulating the heart, increasing blood-pressure, and diminishing secretion.

- Acids.
- Ammonium salts: chloride; carbonate; hydrate (Ammonia).
- Nux vomica.
  - Strychnine.
- Senega.
  - Saponine.
- Squill.
- Balsams: Benzoin; Benzoic acid; Balsam of Tolu; Balsam of Peru.
- Terebinthinates: Wood tar; Terebene; Turpentine; Oleum Pini Sylvestris; Oleum Pini Pumilionis.
- Sulphur.
- Sulphur oils: Onion; Garlic.
- Saccharine substances: Syrups; Liquorice.

Adjuncts.—One of the most powerful adjuncts to expectorants is an **emetic**, which frequently will clear the lungs and save life in cases of chronic bronchitis with impending suffocation, when ordinary expectorants have completely failed.

One of the emetics most commonly employed in such cases is ipecacuanha, either alone or combined with squill, e.g. half a fluid ounce each of ipecacuanha wine and oxymel of squills. When there is great depression, however, and the circulation is very feeble, carbonate of ammonium is to be preferred.

Another powerful adjunct is **warmth** and **moisture** in the room in which the patient is living, and this is best secured by means of steam brought well into the room from a kettle placed upon the hob. The kettle used should either be furnished with a very long spout, as in the case of the ordinary **bronchitis kettle**, or a long tube made of a piece of stout brown paper tied around with a string may be used to convey steam into the room from the nozzle of an ordinary kettle.

Respirators are also serviceable, by preventing the entrance of cold air into the trachea. Many persons, forgetting that the mouth is part of the digestive tract, and that the nose is the proper entrance to the respiratory tract, breathe through their mouth; the consequence is, that the cold air passes down the trachea without being previously warmed. In the nose we have a special arrangement for warming the air. The turbinated bones present an enormous warming surface, like some recently-invented stoves, and moreover, a special arrangement is made for allowing a free flow of blood through this mucous membrane by its being loosely instead of firmly attached to the turbinated bones. Its vessels are therefore capable of great and rapid distension, so as to allow the air to be readily warmed in cold weather.

Most respirators are made simply to go over the mouth, and their advantage is that they force people to breathe through their nose, or warm the air if they cannot do so, and continue to breathe through the mouth. In many persons the same end may be gained by forcing them to wear an invisible respirator. An instrument is sold bearing this name, consisting of a thin plate of metal; but what is perhaps quite as good, or better, is a sovereign or half-sovereign placed between the lips and teeth. Patients are thus forced to keep the mouth shut in order to prevent it from falling out, and its value makes them careful about losing it.

It is often forgotten too that passages and disused rooms are nearly as cold as the external air, and many delicate people who would never dream of going outside in cold weather will, without thinking, walk through cold passages and in rooms without fires. **Warm clothing**, especially over the shoulders, neck, and chest, is very useful, and its utility is recognised by the common employment of so-called chest protectors made of chamois leather and red flannel.

Other adjuncts are **friction** to the chest with stimulating **liniments**; mustard leaves, warm **poultices** and the application of **plasters**; the emplastrum calefaciens (B.P.) or emplastrum picis cum cantharide (U.S.P.) is especially useful in chronic bronchitis.

Arrest of Colds.—Catarrhal affections of the respiratory passages may be excited by irritants of various kinds, and it is probable that these irritants are frequently living organisms. The form of coryza usually called hay-fever is probably due to irritation of the nasal mucous membrane by pollen-grains commencing to grow on it and sending pollen-tubes into its substance.

Other forms of respiratory catarrh, e.g. measles and influenza, are probably associated with specific microbes.

When the respiratory mucous membrane is perfectly healthy it is probable that the invading organisms are quickly expelled or destroyed (p. 85) so that no injury results. But when the resisting power of the mucous membrane is weak, either on account of general constitutional tendencies, or from local and

temporary condition of congestion due to a chill (p. 252), the microbes may begin to grow and cause great irritation.

Among the remedies useful in arresting colds we may recognise **antiseptics**, which destroy microbes, and also **sedatives**, which remove congestion.

Hay-fever has been treated by Binz with a watery solution of quinine in order to stop the growth of organisms in the nose. In some cases this treatment is successful. There is a form of cold sometimes known as influenza-cold. Like true influenza it is extremely infectious and is easily communicated, not only by one member of a family to another, but even by casual visitors. It sometimes begins as a cold in the head, passes down the throat to the trachea and bronchi, leading to severe bronchitis with much depression and occasionally also to gastro-intestinal catarrh. Sometimes it begins in the throat and spreads upwards into the nostrils and downwards into the air-passages. It may frequently be arrested or rendered less severe by the use of dilute carbolic acid applied to the nostrils in the form of spray or by a syringe or nasal douche when the cold begins in the head. When the cold begins in the throat it may be arrested by the use of a carbolic acid gargle, and such a gargle is also useful when the cold begins in the head and is spreading down the throat.

Inhalations of carbolic acid and ammonia appear to be frequently useful in arresting colds. It seems probable that their effect may be due partly to an antiseptic action and partly to their lessening congestion. Carbolic acid inhalations appear to be useful in whooping-cough, probably from an antiseptic action.

Camphor inhaled and also taken internally is useful in arresting colds, though it may be rather hard to give an explanation of its *modus operandi*.

The sedatives which remove congestion of the nasal mucous membrane may be either general or local. Amongst the local may be mentioned bismuth, bismuth and morphine, and cocaine ; and amongst the general, preparations of opium, especially Dover's powder, and aconite.

Selection of Remedies in the Treatment of Cough.

Cough, as I have already said, is a reflex act which is performed by means of a reflex mechanism, and is adopted for the purpose of expelling foreign bodies from the air-passages. It is evident that, when the source of irritation may be removed by efforts at coughing, these efforts are useful, and require to be sustained rather than prevented; but if the irritant cannot be removed, the effort of coughing is injurious rather than beneficial, and the same is the case when the amount of effort is disproportionately great to the good that it effects. In these cases we must try to lessen the cough.

The **source of irritation** in the respiratory passages may either be **free** in the lumen of the bronchial tubes, or may be situated in the **mucous membrane** lining the bronchi, or in the substance of the **lung** itself. Thus we may have foreign substances, such as dust, which have been inhaled, or mucus secreted from the bronchi, resting on the surface of the mucous membrane, and leading to irritation. Such foreign matter may be expelled by coughing, and so may purulent matter lying in a cavity, and the cough may be useful by expelling them.

But if the irritation be simply due to a congested condition of the bronchial mucous membrane; to congestion or consolidation of the lung-tissue itself; to a caseous or calcareous nodule which is firmly embedded in the lung; or to inflammation of the pleura, it is evident that the efforts at coughing will not remove the irritant, but will rather tend to produce exhaustion; and consequently we must either try to remove the source of irritation by other means, or to lessen the irritability of the nervous mechanism by which coughing is produced. Where the cough is due to irritation caused by indigestion we may give alkalies to relieve acidity, but we sometimes find that a blue pill and a black draught are amongst the most efficient remedies for coughs of this character, by the permanently beneficial action they exert on the digestion. When there is irritation of the pharynx, as well as of the trachea, mucilaginous substances, such as jujubes or linseed tea, are exceedingly useful.

Where cough depends on congestion of the mucous membrane of the trachea or bronchi, we not unfrequently find that the inhalation of cold air, by causing contraction of the vessels, and lessening the congestion, will arrest the cough, so that patients are able to walk out on a cold frosty morning for a length of time without coughing. On coming into a warm room the vessels of the respiratory mucous membrane again dilate: the mucous membrane becomes congested, and the congestion leads to violent and prolonged efforts at coughing. In such cases counter-irritation over the neck, upper part of the chest, and between the shoulders is useful, probably by causing contraction of the vessels (p. 252), and thus lessening congestion. But congestion, not only of the trachea and bronchi, but also of the smaller bronchial tubes, may be relieved, not only by counter-irritation, but by inducing secretion. Congestion of the smaller bronchi indicated by loud whistling *râles* all over the chest, is often accompanied by great shortness of breath. The inhalation of hot aqueous vapour tends to relieve the congestion by inducing secretion, but more powerful agents still are antimony, ipecacuanha, and apomorphine. In such a condition as the one just mentioned, where secretion is absent and congestion is great, one or other of these drugs should be given frequently until secretion occurs freely, as indicated by abundant moist *râles* in the chest.

Along with these depressant expectorants, some preparation of opium should be given, in order to lessen the cough, which at this stage is of no advantage. It is advisable not to stop the administration of these expectorants immediately on the occurrence of secretion, but to continue them for some time longer, and gradually to lessen their amount. When secretion has become copious, either from the administration of depressant expectorants or from the natural course of the disease, we have resort to such drugs as will tend to cause its expulsion, and also to lessen its formation. Amongst those which tend to lessen its formation are balsams and terebinthinates (p. 255), and those which tend to assist expulsion have already been mentioned (p. 254). Along with these we generally combine some preparation of opium if the cough is disproportionately severe, and in chronic bronchitis cod-liver oil (p. 254) is perhaps the most efficient of all remedies.

Action of Drugs on the Bronchi.—The bronchi contain muscular fibres in their walls, which appear to maintain a state of tonic contraction similar to that of the arteries. The motor fibres which supply these muscles are contained in the vagi. When one vagus is cut the bronchi of the corresponding lung expand, and when the peripheral end of the cut vagus is stimulated, the bronchi contract so much as sometimes almost to close completely; but the vagi appear to contain bronchial-dilating fibres, as well as bronchial-constricting, so that irritation of the peripheral end of a cut vagus may sometimes cause marked dilatation instead of contraction, and sometimes primary contraction followed by dilatation. The vagi also contain afferent fibres, passing from the bronchi to the nerve-centres, and these afferent fibres have also a twofold action, so that when the central end of one cut vagus is irritated, the irritation may cause either reflex contraction or reflex dilatation of the bronchi in the other lung. It is probable that there are two cerebro-spinal centres: one producing dilatation and the other contraction. Atropine completely paralyses either the constricting fibres of the vagus or their terminations in the bronchi, so that after a very small dose stimulation of the peripheral end of the cut vagus no longer causes contraction. Ether probably paralyses the cerebro-spinal centre for contraction, so that irritation of the central ends of a divided vagus causes expansion instead of contraction in the bronchi of the other lung. Small doses of nicotine have a powerful effect in expanding the bronchi, but the mode of action of the drug has not been determined.[1]

Pathology of Bronchial Asthma.—The attacks of dyspnœa which occur in spasmodic asthma in all probability depend upon spasmodic contraction of the unstriped muscular fibres in the

[1] Roy and Graham Brown, *Journ of Phys.* vol. vi.

bronchi. In some cases no definite cause can be assigned for the occurrence of these attacks, though a gouty tendency in the patient, or the imperfect elimination of waste products, as in renal diseases, increases the tendency to their occurrence. In other cases they appear to be occasioned by irritation, either in the mucous membrane of the respiratory tract or irritation of some other part of the body. Thus they appear sometimes to be brought on reflexly, by irritation of the nose by polypi, by certain odours, or the inhalation of irritating dust, especially pollen of grass, or by congestion of the mucous membrane in ordinary coryza. Sometimes irritation of the pharynx by enlarged tonsils appears to bring them on, and they frequently arise from bronchial catarrh. At other times they may occur in consequence of indigestion, constipation, of worms in the intestine, of disease of the uterus or ovaries, or of pregnancy.

Treatment of Asthma.—In cases where the cause of the attacks can be ascertained, the cause is to be removed. Thus in gouty patients the free use of water as a beverage, and the administration of iodide and bromide of potassium or of salicylate of sodium may be useful. In renal asthma the diet must be chiefly farinaceous and fatty, meat and beef-tea being sparingly given, so as to avoid the accumulation of waste products in the system, and caffeine (pp. 433, 434) may be given to aid their elimination. The asthma of dyspepsia, and also that of constipation, may possibly be due partly to the presence of abnormal digestive products in the blood, as well as to irritation of the mucous membrane of the stomach or intestine. In dyspeptic asthma pepsin has proved very useful; emetics are sometimes of service, probably by removing irritating substances (p. 255), and ipecacuanha may possibly have some special action of its own on the mucous membrane, in addition to its emetic action. Constipation is to be treated by laxatives (p. 388) and cholagogues (p. 404), and worms by vermifuges (p. 408). Polypi in the nose and enlarged tonsils are to be removed, and for congestion of the mucous membrane of the nose or throat, carbolic acid lotion may be used (p. 257).

The medicine most usually employed to prevent recurrence of the attack is lobelia inflata. The exact mode of action of this drug is not known, but the general symptoms produced by it so closely resemble those of tobacco that it is often known as Indian tobacco, and possibly its action on the bronchial tubes may be somewhat the same as those of nicotine. During the attacks of spasmodic asthma more relief is usually afforded by the inhalation of smoke of various kinds than by any other means. The smoke of tobacco, of the leaves of various species of datura, of paper impregnated with potassium nitrate, or with a mixture of potassium nitrate and chlorate; of pastiles and of various powders, which probably are principally composed of powdered datura-

leaves, mixed with powdered nitre, and perhaps, also, with ipecacuanha, all prove useful. The action of all these smokes is probably the same as that of nicotine, for Vohl and Eulenberg[1] have shown that the active principles in tobacco-smoke really are not nicotine alone, but are the products of the dry distillation of tobacco-leaves, consisting chiefly of pyridine, collidine, and allied substances, which resemble nicotine in action, and are present along with it in the smoke. The same products, but in different proportions, are obtained by the dry distillation of other organic bodies. The proportion in which the different bases are present depends both on the nature of the substances subjected to dry distillation, and on the amount of oxygen present during the process. When much oxygen is present, bodies of higher atomic weight and less volatile than those lower in the series are formed, much collidine being produced when tobacco is smoked as a cigar, while pyridine is the chief product when it is smoked in a pipe. It is probable that the admixture of nitre with paper or with powdered leaves acts beneficially by producing a different mixture of organic bases than would be produced by burning the paper or the leaves alone, and that we must look to bodies allied to collidine for the relief of asthma.

[1] *Arch. Pharm.* (2), 1873, vol. cxlvii. 130–166.

CHAPTER XI.

ACTION OF DRUGS ON THE CIRCULATION.

It has already been mentioned that the cells of which higher organisms are composed live in the intercellular fluid or lymph which bathes them.

This nutritive fluid is continually being renewed by fresh supplies exuding from the blood-vessels into the lymph-spaces which surround the cells, the excess being removed by absorption either by the veins or by the lymphatics. Besides this, an interchange of gases (internal respiration) and of solids takes place by diffusion between the lymph and the blood.

When the circulation stops, internal respiration is arrested, and the cells die. But they do not all die at the same time, for some are able to live longer without fresh supplies of oxygen than others. The order in which they die is (1) the cells of the initiative nerve-centres, as the brain; (2) those of the automatic and reflex centres; (3) nerve-fibres (which are modified nerve-cells); (4) unstriated muscles; (5) striated muscles.

Arteries and Veins.—It is important in this respect to remember that it is only so long as blood is in the arteries that it is available for the nutrition of cells. Once in the veins it is useless for nutrition; and were it not that it readily passes from the veins into the arteries again, it might as well be outside the body for any purposes of nutrition.

The veins are very capacious, and when dilated to their utmost, they can alone hold all the blood the body contains, and more. During life they are constantly kept more or less in a state of contraction by the action of the nervous system, but when they become completely dilated, as after death, all the blood flows into them, leaving the arteries empty. It is therefore possible, as Ludwig has well expressed it, to bleed an animal into its own veins. Schiff has shown that when the blood-vessels relax as they do after section of the medulla oblongata, the whole of the blood of another animal as large as the one experimented upon must be introduced in addition to its own, in order to raise the pressure within the vessels to the normal. Even this is insufficient to keep up the pressure, for the vessels go on still dilating, and the pressure falls, notwithstanding the large quan-

tity of blood which is present in them. It is therefore evident that the normal action of the **vaso-motor centres** is more than equivalent, for the purposes of circulation, to as much blood again as the animal possesses. Weakened power of these centres is to a certain extent equivalent to bleeding, and increased power has a similar effect to an increase in the quantity of blood in the vessels.

Blood-pressure.—The continuity of the circulation of blood through the capillaries is not maintained by the heart alone: the elastic pressure of the arteries on the blood within them plays a most important part, and indeed during the cardiac diastole the circulation is maintained entirely by this elastic pressure.

If the arterioles or capillaries through which the arterial system empties itself into the veins are much contracted, so that the blood can flow only slowly through them, the heart may stop, and yet the blood-pressure may remain for many seconds almost unchanged. But if the arterioles or capillaries are dilated, the arteries quickly empty themselves into the veins, arterial pressure rapidly falls, and circulation soon stops.

FIG. 83.—Diagram to illustrate the effects of the horizontal and vertical position on the circulation of the frog in shock. *a*, normal circulation in the upright position. *b*, circulation after dilatation of the veins has been produced by a blow on the intestines. The blood does not reach the heart, and it beats empty, so that the circulation stops. *c* shows the circulation in a horizontal position after the veins have been dilated, as in *b*. The veins are still dilated, but the blood reaches the heart, and the circulation is carried on. Fig. *c* is perhaps too diagrammatic, as it appears to show an empty space or air in the veins. In reality the veins, being very thin-walled, collapse. Fig. *b* is open to the same objection, but if we suppose ourselves to be looking at the vein from the front instead of in section, *b* represents almost exactly what I have myself seen in repeating Goltz's experiment.

I use the words arterioles and capillaries as synonymous, because it is almost certain that the capillaries do contract. In most cases where contraction has occurred in the peripheral vessels, it is difficult or impossible to say whether its seat is in the capillaries or arterioles.

The action of the heart is to pump the blood out of the veins into the arteries, and this it can only do when the blood reaches it. If the veins are much dilated and the animal is in an upright position, no blood may reach the heart, or so little blood that its pulsations are practically useless. This is seen in the frog when dilatation of the large veins has been reflexly produced by striking the intestines (Fig. 83*b*). When the animal is laid flat, the blood flows into the heart, and then it works normally. It is probable that a similar condition occurs in man, as one of the factors in shock; and in this condition, as well as in fainting, or failure of the heart's action from the effect of drugs,

as chloroform, or other causes, the person should be laid flat, with the limbs raised so that the blood may flow out of them into the heart, and with the head low (either perfectly level with the body or depressed below it), in order to permit of an increased supply of blood to the intra-cranial nerve-centres.

Fainting and Shock.—In **fainting** there is sudden unconsciousness, which appears to be caused by sudden arrest of the supply of blood to the brain. This arrest may be due to a rapid fall in blood-pressure, either from stoppage of the heart, rapid dilatation of the arterioles, or sudden removal of pressure from the larger vessels. It is possible that these conditions may be associated with spasmodic contraction not only of the vessels of the face and surface generally, but of those supplying the brain itself. The effect of sudden change from a horizontal to an upright posture in producing syncope has already been mentioned (p. 205). Sudden removal of external pressure from the great vessels acts upon both arteries and veins. It removes external support from the arteries, and allows them to yield more readily to the influence of the blood-pressure, and by their dilatation to lessen it. It allows the large veins also to dilate, and blood to stagnate in them. Its influence is readily seen when fluid is removed too suddenly from the abdomen, and external pressure by a bandage not supplied in its place, as in cases of ascites.

It is seen, perhaps, even more strikingly, where the bladder has been allowed to become distended and is suddenly emptied. The effect of this is shown in Fig. 84. In *a* the bladder is repre-

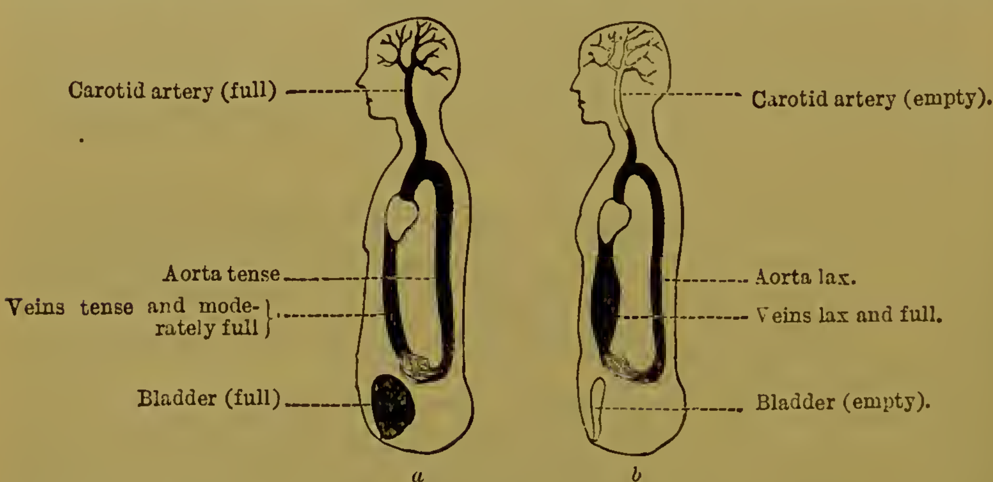

FIG. 84.—Diagram to show the effects on the cerebral circulation of rapidly emptying the bladder.

sented as full, and, the pressure within the abdomen being considerable, the veins are prevented from dilating, the heart is well supplied with blood, and the circulation in the brain is active. In *b*, the bladder is represented as empty, and the abdominal contents being diminished, so that the intra-abdominal pressure is lessened, not only do the aorta and other vessels become lax from loss of the external pressure, but the veins dilate, the heart

is imperfectly supplied with blood, the cerebral circulation fails, and syncope ensues. This occurs more readily just after waking, before the vaso-motor centre has recovered its usual tone, so that one of the most favourable conditions for its occurrence is when a man jumps suddenly into the upright position and empties his bladder immediately on waking. The consequence of this sometimes is that he falls down suddenly, quite insensible, during the act of micturition. I have seen one case in which the tendency appeared to be increased by the practice of opium-eating, probably from the diminished excitability of the vaso-motor centre produced by the drug. It is evident that the danger will be increased if the intervals between the systoles of the heart are prolonged, and it is the combination of the natural tendency to syncope, produced by large doses of digitalis, with that caused by the sudden assumption of the upright posture, and by the rapid emptying of the bladder, which renders micturition in the upright posture so excessively dangerous in persons under the action of digitalis, and leads so frequently to death.

It is evident that **fainting** may be **prevented** by increasing the blood-pressure in the brain locally, or throughout the body generally. To increase it locally the head of a fainting person should be allowed to lie level with the body, or a little below it, and on no account raised even by pillows. A fainting fit may indeed often be prevented by sitting with the head hanging between the knees. It may also be prevented or removed by such conditions as raise the general blood-pressure, e.g. a draught of cold water, which causes contraction of the gastric vessels, or a sniff of ammonia or acetic acid, which stimulates the nasal nerves, and causes reflex contraction of the vessels generally. In some parts of India the natives are accustomed to bring persons round from a faint by compressing the nostrils and holding the hand over the mouth, so as completely to stop respiration. The accumulation of carbonic acid in the blood irritates the vaso-motor centre, raises the blood-pressure, and thus probably tends to bring the person round.

In **shock** there is no unconsciousness, but the failure of the circulation is even more profound than in syncope. Its pathology is not perhaps exactly ascertained, but it probably depends to a great extent on a paralytic distension of the great veins, as in Goltz's experiments. I have found that in shock produced in a similar manner in a rabbit the blood-pressure could be raised from two inches up to two and a half by the inhalation of ammonia.

Schema of the Circulation.—In order to understand the action of drugs on the circulation it is absolutely necessary to have a clear idea regarding the effect of the heart and capillaries in maintaining the blood-pressure. This is best obtained by using a schema which can be easily made from a spray-apparatus (Fig. 85). By removing the glass or metal tube from one of these,

and attaching a nozzle with a small stopcock to the india-rubber tube in its stead, we obtain a very good schema of the circulation; and, by imitating on it the changes which occur in the heart and vessels, we may form a much clearer idea of them than we could otherwise do. The india-rubber ball will represent the heart; the elastic bag, surrounded by netting, will represent the elastic aorta and larger arteries; and the stopcock, which regulates the size of the aperture through which the air escapes, will represent the small arteries and capillaries, whose contraction or dilatation regulates the flow of blood from the arteries into the veins. We may judge of the tension in the arteries by the distension of the bag, or still better, we may connect the tube between it and the stopcock with a mercurial manometer, and estimate the tension by the height of the mercurial column which it sustains. If we turn the stopcock so as to present some resistance to the escape of air, and then compress the india-rubber ball, very little air will issue from the

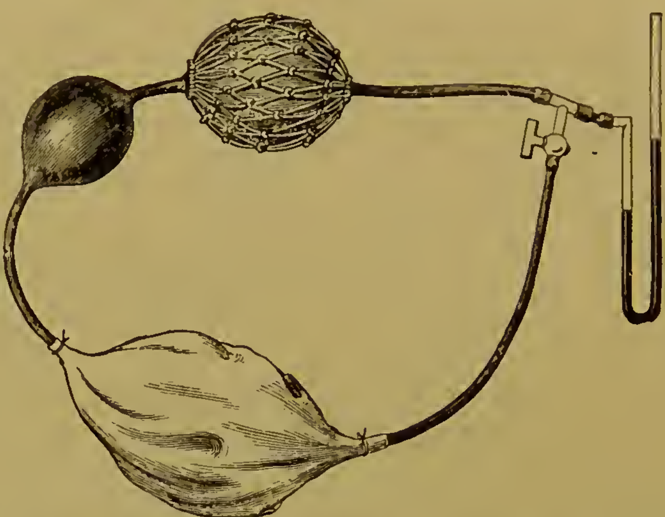

FIG. 85.—Simple schema of the circulation, consisting of a spray-producer, bladder, and mercurial manometer. The elastic ball represents the heart; the elastic bag, covered with netting to prevent too great distension, represents the aorta and arterial system, and the bladder represents the venous system.

stopcock even while we are squeezing the ball; the greater part of it goes to distend the bag; and, when we cease to compress the ball, very little air passes through the stopcock. At the next squeeze, the bag becomes a little more distended; and a little more air passes through the stopcock, not only while we are compressing the ball, but even when we relax our grasp. At each squeeze of the ball, the elastic bag becomes tighter, till it is so tense, and contracts so strongly on the air inside, that it can press all the extra amount of air, forced into it when the ball was compressed, through the stopcock during the time when the ball is relaxed. When this is the case, every time we squeeze the ball we see the bag become a little fuller, and air issue more quickly from the nozzle. At each relaxation, while the ball is refilling, the bag gets a little slacker, and the air passes out of the nozzle a little more slowly, but never stops entirely. During the time the ball is filling, the valves between it and the bag and nozzle are closed, and cut it off from any connection with them. All this time, then, the stream of air from the nozzle must be entirely independent of the ball; it is produced by the contraction of the elastic bag, and by it alone. The bag may be stretched, and the tension of its walls increased in consequence, in two ways: first, by working the ball more quickly or compressing it more completely; second, by lessening the opening of the nozzle, and thus hindering the passage of air through it. One trial will, I think, be enough to show how much easier it is to alter the pressure by changing the size of the nozzle than by any alteration in the working of the ball, and to prove that alterations in blood-pressure

probably depend much more on alterations in the lumen of the small arteries than on changes in the action of the heart.

But our schema, as it at present exists, is not a perfect representation of the heart and vessels; for it draws its air from an inexhaustible reservoir, the atmosphere, and is not obliged each time to use that amount alone which it had previously driven through the nozzle; while the heart can only use the blood which has been forced by it through the capillaries and returned to it by the veins. In order to make our schema complete, we must connect its two ends by tying them into a bladder or large thin caoutchouc bag (such as is used, after inflation, as a toy for children), so that the air shall pass into it from the nozzle and be sucked out of it by the elastic ball. This will represent the veins. If we then repeat the experiment just described, we shall find that, when we begin to work the ball and stretch the elastic bag representing the arteries, the bladder representing the veins becomes empty and collapsed; and just in proportion as we fill the bag do we empty the bladder. If we now stop, the air will gradually escape from the bag to the bladder, till the air in both is of equal tension, as at first.

Circulation in the Living Body.—The phenomena of the circulation in the heart and vessels are very much the same as in the schema. When the heart stands still (as when the vagus is strongly galvanised), the blood flows from the arteries into the veins until the arteries are nearly empty and the pressure within them falls to zero. If the heart now begin to beat, it forces blood into the elastic aorta and arteries at each systole, and distends them, just like the elastic bag of the schema; while at the same time it takes blood from the veins, and they become empty in proportion as the arteries become full. During every diastole of the heart, the distended aorta and other arteries, in virtue of their elasticity, contract on the blood they contain, and keep it flowing on through the capillaries till another systole occurs; the heart, meanwhile, being completely shut off from the aorta by the sigmoid valves (just as the ball of the schema was shut off from the elastic bag). In general, the diastole is longer than the systole; so that for the greater part the circulation through the capillaries is carried on by the elasticity of the arteries, and not directly by the heart. The arteries, which we have supposed to be at first empty, gradually become distended by the heart, just as the elastic bag was by the ball, and exert more and more pressure on the blood in them (so that it would spout higher and higher if one of them were cut), till they are able during the diastole to press the same amount of blood through the capillaries into the veins as had been pumped into them during the systole. The more tensely they are stretched, the greater is the pressure they exert on the blood they contain; and the amount of this is termed the **arterial tension** or **blood-pressure.** These two terms mean the same thing, and we use one or other just as the fancy strikes us. At each systole, the fresh supply of blood pumped in by the heart stretches them more; that is, the arterial tension rises. During each diastole, the blood escapes into the wide and dilatable veins, and the arteries

become less stretched; that is, the arterial tension falls. This alternation of rise and fall constitutes the **pulse**.

Besides the **oscillations** which take place in the blood-pressure at each beat of the **heart**, a rise and fall in the form of a long wave occurs at each **respiration**. The wave begins to rise just after inspiration has begun, reaches its maximum just after the beginning of expiration, and then begins to fall again till a new wave succeeds it. The heart-beats are generally quicker during inspiration, and slower during expiration.

The blood-pressure thus oscillates up and down at each heart-beat and rises and falls with each respiration, and the average between the highest and lowest points is called the mean arterial tension or **mean blood-pressure**.

Besides the oscillations in blood-pressure due to the pulse and to the respiration, there are slowly rising and falling waves to which the name of **Traube's curves** is given. These are due to alternate contraction and relaxation of the arterioles and capillaries. Rhythmical contraction of the arterioles has been observed in almost all parts of the body of rabbits, and probably occurs both in the lower animals and in man.

The blood-pressure is not equal throughout the whole arterial system. It is greater in the large and less in the smaller arteries, in which it becomes diminished by the friction between the blood and the arterial walls. It is also modified by gravity, so that the position of a limb may alter the pressure in its arteries.

Method of ascertaining the Blood-Pressure.

The blood-pressure is usually estimated in animals by connecting a large artery, such as the carotid or femoral, with a bent tube containing mercury by means of a connecting tube, which is filled with a solution of carbonate of sodium to prevent coagulation. The pressure is estimated by the height at which the mercury stands in the outer limb of the tube. The height may either be read off with the eye, or, what is much better, it may be registered on a revolving cylinder by means of a long float which rests upon the surface of the mercury, and bears on its upper end a brush or pen. This method, which is important both in itself and as being the introduction of the graphic method into physiology, we owe to C. Ludwig. The apparatus is known as the **kymograph**.

Tracings may be taken upon paper with a varying speed: it is usual to take them upon paper travelling rapidly, so that quick and small oscillations due to the cardiac beats may not be lost or obscured by fusion. The great disadvantage of this is that it is impossible to use the curves directly: they must be reduced, and this is a work requiring much time and labour. When taken on a slowly revolving cylinder we get the general results of the action of a drug on the blood-pressure shown us at a glance; and its effects on the form and rapidity of the pulse may by a little arrangement be recorded from time to time on another cylinder revolving more rapidly.

This method gives us both the blood-pressure and the oscillations which it undergoes on account of the cardiac pulsations and respiration. If we wish to get the mean blood-pressure unaffected by these oscillations, it is

done by simply narrowing at one point the calibre of the tube containing the mercury, either by a stopcock, or by reducing the tube to a capillary bore.

Fallacies of Mercurial Manometers.—The oscillating mercurial column does not give the variations in blood-pressure quite truly, because the oscillations are compounded of these variations and of the oscillations due to the inertia of the mercury itself. In order to obtain the exact form of variation we employ Fick's kymograph (Fig. 86), or Roy's tonometer, in which the apparatus is made very light, and all oscillations due to its own inertia are as far as possible avoided.

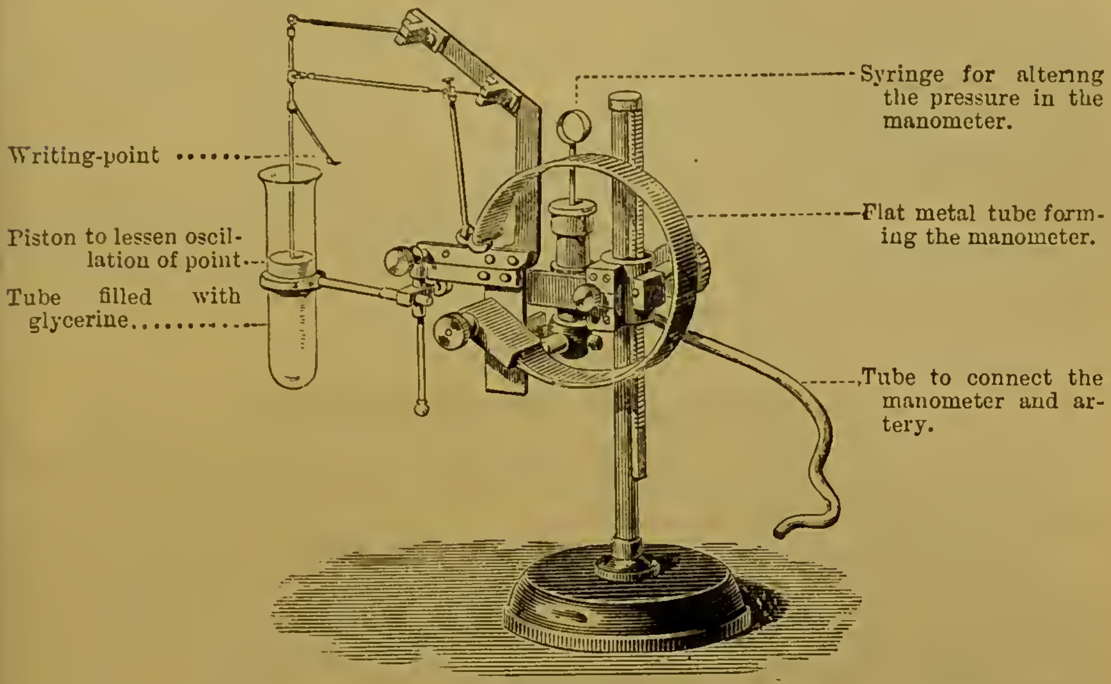

FIG. 86.—Fick's kymograph. It consists of a flat metal tube, bent into a nearly circular form, filled with alcohol, and connected with the artery by means of a leaden tube. filled with a solution of sodium carbonate. When the pressure increases within it, the tube straightens, and when the pressure diminishes it bends. These changes are magnified and recorded on a cylinder by a light lever. The vibrations of the lever are lessened by a piston, which works in a tube filled with glycerine.

Fallacies from Anæsthetics.—Even if the instrument be free from fallacy, we still have difficulty in ascertaining the real action of the drug on the circulation, inasmuch as the blood-pressure is much affected by movements, and by anæsthetics. If the animal is not anæsthetised we may get untrustworthy results from the straining or movements it may make, and if it is anæsthetised, the anæsthetic may greatly alter the power of the heart, or the sensibility of the nerve-centres either to the direct action of the drug upon them, or to its reflex action through the afferent nerves. In order to get rid of movement, and at the same time to prevent the vascular centres from being much depressed, curare is sometimes used instead of an anæsthetic. Perhaps, almost equally good results may be obtained by using ether as the anæsthetic, carefully regulating the supply so as to abolish sensation without greatly affecting the medulla. The reasons why this is possible are discussed at p. 204. In order to regulate the supply of ether, we use a stopcock, by which pure ether, or pure air, or an admixture of both in any desired proportion, can be passed into the lungs (Fig. 73, p. 211).

Other fallacies arise from the mode of injecting the drug, and this has sometimes led to false results: thus drugs are not unfrequently injected into the jugular vein, as it is very conveniently situated for the purpose. In this way, however, they are carried directly to the heart, and act much more strongly upon it, than they would do if absorbed from other parts of the body. In the case of irritant salts, for example, time is not afforded for their irritant properties becoming lessened by chemical combination with the constituents of the blood. If the solution injected contain particles which will

not pass through the pulmonary capillaries, or if it is likely to cause coagulation of the blood, it may plug up the pulmonary vessels and give rise to dyspnœa and convulsions.

Both these objections are avoided when the drug is injected under the skin, or into the peritoneal cavity. Absorption from the skin is slower than from the peritoneum. In some experiments this is a disadvantage: in others, however, it is an advantage.

Another fallacy sometimes arises from the solution of carbonate of sodium used to prevent coagulation. In order to prevent the blood from passing too far into the tube connecting the artery with the kymograph, it is usual to introduce the solution of carbonate of sodium into the tube by a syringe (*vide* Fig. 86) or otherwise, under a pressure very little less than the usual blood-pressure of the animal experimented on. If the blood-pressure be lowered much by stoppage of the heart or dilatation of the vessels, the solution of carbonate, or bicarbonate of sodium, runs into the arteries and may cause convulsions and death. Thus stoppage of the heart by irritation of the vagus, or by the action of a drug, may sometimes appear to be followed by results which are not really due to it, but only to the conditions under which the experiment has been made.

Alterations in Blood-pressure.

In speaking of blood-pressure, arterial blood-pressure is always meant, unless otherwise stated.

As the blood-pressure depends on the difference between the quantity pumped into the arterial system by the heart at one end, and the quantity flowing out through the arterioles into the veins at the other in a given time, it is evident that—

The **blood-pressure** will remain **constant** when these quantities remain equal to each other.

It will **rise** when—

(*a*) More blood is pumped in by the heart.

(*b*) When less flows out through the arterioles in a given time.

It will **fall**—

(*a*) When less is pumped in by the heart; or,

(*b*) More flows out through the arterioles; or, to look at it another way:—

Heart	more active.	Blood-pressure		rises.
	less ,,	,,	,,	falls.
Arterioles	contract	,,	,,	rises.
	dilate	,,	,,	falls.

The heart may throw more blood into the arteries, either by pulsating more rapidly, or by pulsating more vigorously and more completely, so that at each contraction a larger amount of blood is expelled. But increased activity can only affect the blood-pressure so long as there is a free supply of blood entering the heart. If there exist any obstruction to its entrance the increased cardiac action will have no effect. Hence obstruction of the pulmonary circulation will also lower the blood-pressure.

The causes of alteration in the blood-pressure may be tabulated as follows :—

Blood-Pressure

May be raised—	May be lowered—
1. By the heart beating more quickly.	1. By the heart beating more slowly.
2. By the heart beating more vigorously and more completely, and sending more blood into the aorta at each beat.	2. By the heart beating less vigorously and completely, and sending less blood into the aorta at each beat.
3. By contraction of the arterioles, retaining the blood in the arterial system.	3. By dilatation of the arterioles, allowing the blood to flow more quickly into the veins.
	4. By deficient supply of blood to the left ventricle, as from contraction of the pulmonary vessels, or obstruction to the passage of blood through them, or from stagnation of blood in the large veins, e.g., in shock.

The influences on the pressure exerted by (*a*) the number of beats, and (*b*) by the amount of blood sent out by the heart at each beat, to a certain extent, though by no means completely, counteract each other; for, when the heart is beating quickly, it has not time to fill completely, and so sends out little blood at each beat: but, when beating slowly, it becomes quite full during each diastole, and sends out a larger quantity of blood at each contraction.

It is evident that the amount of blood which the heart can send into the arteries at each beat will depend also upon the completeness with which the ventricle relaxes during diastole. If the relaxation be incomplete very little blood will enter the ventricle, and thus a drug which increases the contractile power of the heart may, by unnecessarily prolonging the systole, lower the blood-pressure as much as a drug which paralyses the heart and prevents the ventricle from expelling its contents.

Relation of Pulse-rate and Arterioles to Blood-pressure.

Although we are unable, from the mere fact that the blood-pressure rises or falls after the administration of a drug, to say whether the result is due to the action of the drug on the heart or on the arterioles, yet we can come to some general conclusion regarding its mode of action by comparing the alterations which

it has produced in the blood-pressure with those which occur in the pulse-rate. For in the normal condition of an animal, when all the nerves are intact, a rise in the blood-pressure renders the pulse slow by increasing the normal tone of the vagus centre in the medulla, and a fall of blood-pressure quickens the pulse by diminishing the tone. This mechanism tends in the normal animal to keep the blood-pressure more or less constant.

We find, therefore, that when alterations in blood-pressure and pulse-rate are depicted graphically, so that a rise in one curve indicates a rise in blood-pressure, and a rise in the other

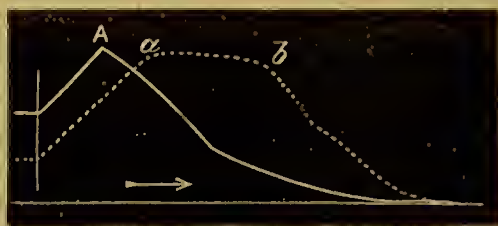

FIG. 87.—Diagram of a pulse and blood-pressure curve, where the alterations are due at first to the action of a drug on the heart, as in the case of atropine. The unbroken line indicates the blood-pressure, and the dotted line the pulse. After the injection shown by the vertical line the vagus is paralysed, the pulse becomes very rapid, and the blood-pressure rises. At A the vaso-motor centre becomes paralysed, the arterioles dilate, and the pressure falls. From *a* to *b* the action of the heart continues nearly uniform, notwithstanding the fall in blood-pressure, but at *b* the heart begins to become paralysed, and the pulse-rate and blood-pressure both continue to fall steadily till death.

indicates quickening of the pulse, the two **curves** run in **opposite** directions if the alteration in blood-pressure is due to the **arterioles**, but they run **parallel** when the alteration is due to the **heart** (Fig. 87). Thus, if the vagi be cut, we find that the pulse-rate rises, and in consequence of this the blood-pressure also rises. Here the alteration in pressure is due to the heart, and the two curves are therefore parallel. If the vagi be irritated the pulse-rate falls, and in consequence of this the blood-pressure also falls. Here again the alteration is due to the heart, and the two curves are parallel.

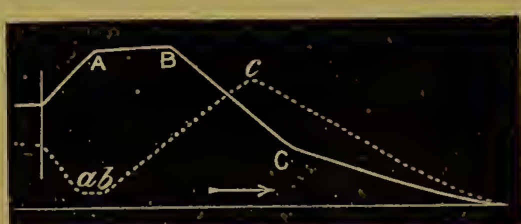

FIG. 88.—Diagram of pulse and blood-pressure curves, where the alterations are due at first to the action of a drug on the arterioles. The unbroken line indicates the blood-pressure, the dotted line indicates the pulse. The upright line indicates the time of injection of the poison. This is followed by contraction of the arterioles and consequent rise of blood-pressure. This rise stimulates the vagus roots, and causes slowness of the pulse. At *b* the vagus becomes paralysed, the pulse becomes quick, and the pressure rises still higher between A and B. At B the vaso-motor centre becomes paralysed, the arterioles dilate, and the pressure falls, notwithstanding the rapidity of the pulse. At *c* the heart itself begins to be paralysed, its beats become slow, and both pulse and pressure fall steadily till death.

If, on the other hand, the arterioles are made to contract the pressure rises, but the increased pressure stimulates the vagus roots in the medulla and the pulse-rate falls, so that the curves

run in opposite directions. If the arterioles dilate the pressure falls, and the vagus tone being lessened the pulse-rate rises; so the curves are again in opposite directions (Fig. 88).

An example of this is seen in the accompanying curve (Fig. 89), which illustrates the action of erythrophlœum—a substance similar in action to digitalis—on the circulation. After the injection of the drug the vessels contract, and the blood-pressure consequently rises and produces some slowness of the pulse. In a little while the vagus becomes paralysed, the pulse becomes quicker, and

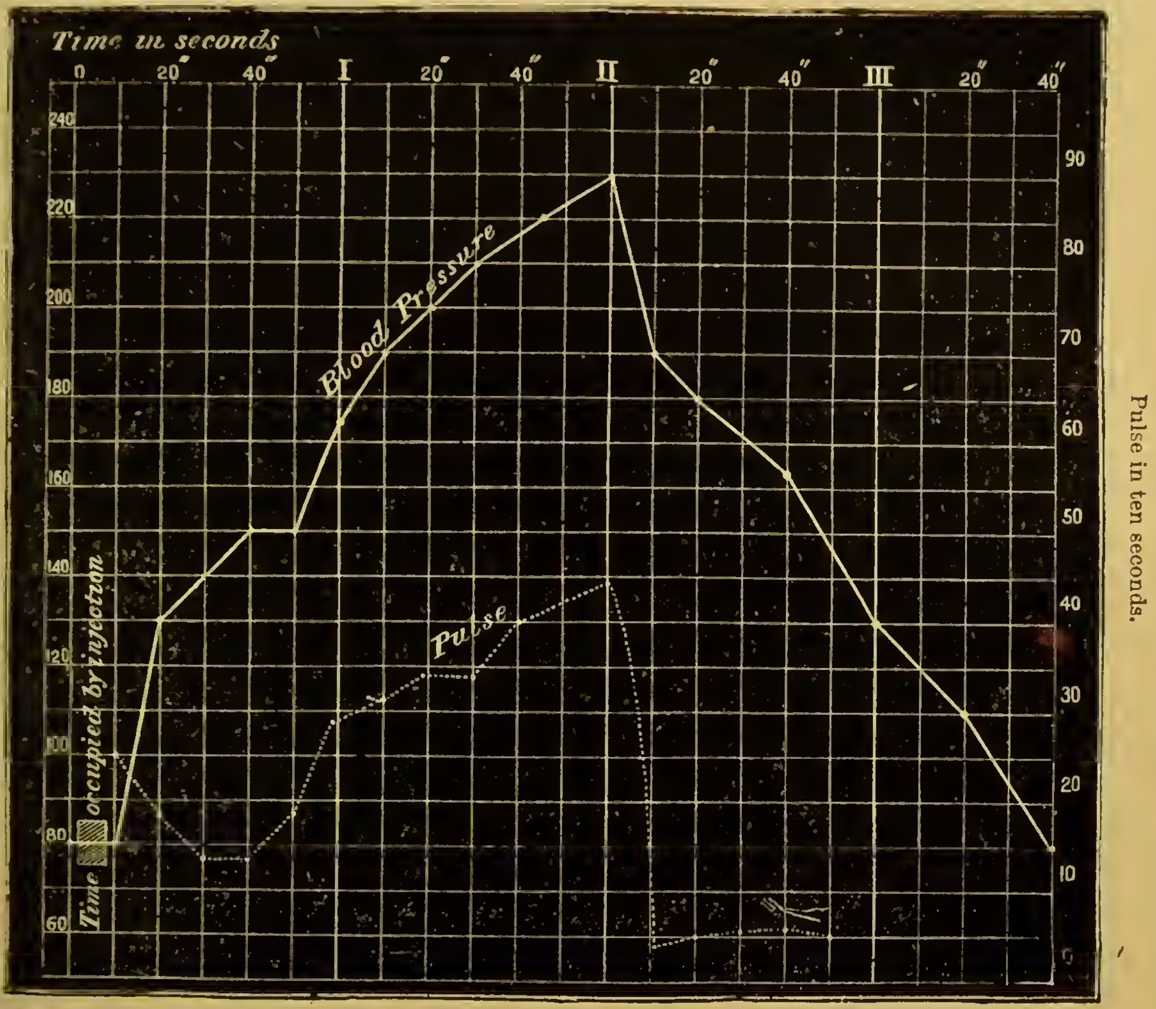

FIG. 89.—Curve of the pulse and blood-pressure in a cat after division of the spinal cord at the atlas and injection of erythrophlœum. (From a paper by Brunton and Pye, *Phil. Trans.* vol. 167.)

the pressure rises still further. At a later stage the heart becomes slow, apparently from the action of the drug upon it, and the blood-pressure then falls again. At first then, where the alteration of pressure depends upon the state of the vessels, we have the two curves running in opposite directions, but when the alterations depend upon the condition of the heart we have them running parallel.[1] It will be noticed that in the latter part of the curve, although the blood-pressure and the pulse sink

[1] Although the rise in blood-pressure which accompanies that of the pulse is partly due to the heart, it is very probable that the contraction of the arterioles which caused the rise at first is not only continuing but increasing.

together, they do not sink quite parallel; the pulse falling very rapidly and the blood-pressure very slowly. From this fact we may conclude that the arterioles are still contracted, and this affords an illustration of another way in which we judge of the effect of drugs upon the arterioles. This conclusion would not be warranted by the data contained in Fig. 89 alone. For the slowness with which the blood-pressure falls in this experiment might possibly be due to the heart beating more perfectly, at the same time that it begins to beat more slowly. An examination of the original tracings of the blood-pressure shows that this is not the case and that the beats of the heart became feeble at the same time that they became slow.

The mutual regulating power of the pulse and blood-pressure only exists when the vagi are working normally. If they should be paralysed, either by section or by the action of a drug, increased arterial pressure will no longer slow the pulse; it may even quicken it, and therefore the pulse-rate and blood-pressure may, in such a condition, run parallel even though the increased pressure should be dependent upon alterations in the arterioles.

But if the vagi are not paralysed, and we find on comparing the curves of blood-pressure and pulse-rate that they run parallel, a fall in the blood-pressure and slowness of pulse occurring together, or a rise in pressure and quickness of pulse accompanying each other, we may conclude that the alterations in such a case are due to changes in the action of the heart.

If, however, we find that the curves run in opposite directions, the pressure rising and the pulse falling, it is highly probable that the rise is due to contraction of the arterioles, and that the fall of the pulse is caused by the rise of pressure acting as a stimulus to the vagus roots. This is, however, not quite certain, as it might be due to the action of the drug upon the vagus, and the proper method of ascertaining this would be that employed by Ludwig, of allowing a quantity of blood to flow out into a bladder connected with a blood-vessel, so that the pressure should fall. If the pulse still continued slow in spite of the fall of pressure, it would be evident that the slowness was due to the action of the drug upon the vagus, and not to indirect action through the blood-pressure. By employing a bladder in this manner the blood can be quickly introduced again into the vessels after the effect of its withdrawal has been ascertained.

We not unfrequently find that, owing to the action of a drug the pulse, which has become slow during the rise of the blood-pressure, suddenly becomes very rapid notwithstanding that the pressure continues high. This is usually due to paralysis of the vagus-ends in the heart, and, when this occurs, the correctness of the conclusion which we draw from the occurrence may be ascertained by stimulating the vagus in the neck by a faradaic current, and seeing whether any slowing or stoppage of the heart

occurs. Frequently we find that after the pulse has become quick from paralysis of the vagus, the pressure which the quick pulse had raised begins to fall again from paralysis of the arterioles. The pulse may continue quick and weak almost till death and then cease suddenly, or it may become gradually slow as well as weak from paralysis of the heart itself.

Effect of the Arterioles on Pulse-curves.—The influence of the arterioles upon the blood-pressure in a living animal can be to a great extent ascertained by the rapidity or slowness of the fall of the blood-pressure during the diastole of the heart. When the heart is beating slowly the diastole may be long enough to show distinctly the curve which the blood-pressure describes during its descent; but if the heart is beating quickly the diastole may be so short that this curve cannot be exactly obtained. It is then necessary to prolong the diastole artificially by stimulation of the vagi.

The reason why the part which the arterioles play in maintaining the blood-pressure can be ascertained by the way in which it falls during cardiac diastole, natural or artificial, is that in the healthy heart the aortic valves close during the diastole so as to separate the aorta completely from the ventricle.

In considering the blood-pressure during the diastole, we may therefore disregard the heart entirely, and look upon the aorta and its branches as an elongated elastic bag closed at its cardiac end, but open at its capillary end. This bag is distended with blood, which in consequence of the elastic pressure exerted upon it by the arterial walls tends to flow out into the veins. The rate at which it does this will depend—

1st, on the elastic pressure or arterial tension; and,

2ndly, on the size or degree of contraction of the arterioles or capillaries.

If we connect a manometer with this elongated bag as in Fig. 90, and place on the mercurial column a float by which its

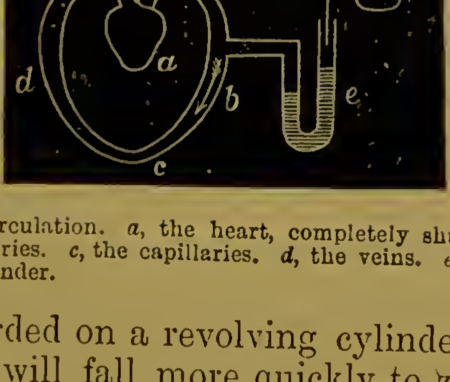

FIG. 90.—Diagram of the circulation. *a*, the heart, completely shut off by the valves during diastole from *b*, the arteries. *c*, the capillaries. *d*, the veins. *e*, mercurial manometer. *f*, a float. *g*, a recording cylinder.

height can be recorded on a revolving cylinder, it is evident that the pressure-curve will fall more quickly to zero when the capillaries are dilated, and more slowly when they are contracted.

With capillaries of the same size, the rate of flow will vary

with the arterial pressure. If the pressure be high the curve will fall more rapidly than when it is low, for the greater blood-pressure will drive the blood more rapidly through the open arterioles. If we find that with a normal pressure the pressure-curve falls more slowly than usual during the diastole, we may conclude that the arterioles are contracted; and if we find that the fall is slower, notwithstanding that the pressure is higher than usual, the proof that the arterioles are contracted is so much the stronger.

This is what Meyer and I[1] observed in the case of digitalis, where we found, as in the accompanying figure (Fig. 91), that the fall of the blood-pressure during the cardiac diastole in a dog is much slower after than before the injection of digitalis into the circulation.

In observations of this sort it must always be borne in mind that a great difference exists between the vessels of the intestines

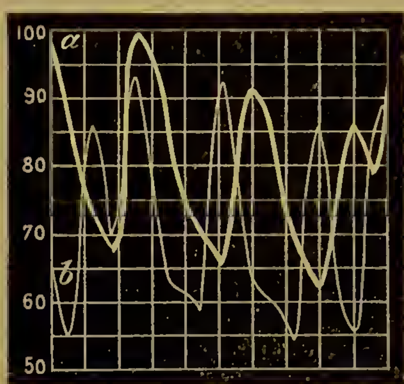

FIG. 91.—Tracing showing the blood-pressure and form of the pulse-wave before and after the injection of digitalis in the dog. The thin line shows the blood-pressure before, and the thick one after, the injection. The curve sinks more slowly after the injection, notwithstanding the greater pressure in the vessels.

on the one hand, and those of the muscles on the other. The former are readily controlled by the vaso-motor centre, and when this is stimulated they contract greatly. Those of the muscles appear to be but slightly influenced by the vaso-motor centre, so that when it is stimulated they hardly contract at all, and indeed the flow of blood through them becomes accelerated on account of the contraction of the vessels elsewhere. When the vaso-motor centre is stimulated at the same time that the vagus is irritated, the blood-pressure appears to fall nearly as quickly as when the vagus alone is irritated. It seems possible, however, that this result may be really due to some extent to actual dilatation of the vessels in the muscles, for stimulation of the motor nerves of muscle appears to produce a vaso-dilating effect on their blood-vessels (Gaskell and others).

The want of power of the vaso-motor centre over the vessels

[1] Brunton and Meyer, *Journal of Anatomy and Physiology*, vol. vii. 1872, p. 134. The experiments described in the paper were performed in 1868.

of the muscles is probably of considerable pathological importance. John Hunter[1] noticed, when he was bleeding a lady from a vein in the arm, that the blood, which previously had been dark and venous, became bright scarlet, like arterial blood, when she fainted, and remained so during the continuance of the faint. This seems to indicate that during syncope, although the superficial vessels are empty and contracted, the arterioles of the muscles are dilated like those of an actively secreting salivary gland.

If we find, then, that after the injection of a drug the blood-pressure remains constantly high, during stoppage of the heart, we may conclude that the vessels of the muscles are contracted as well as those of the intestine. Such a condition occurs after the injection both of digitalin and of erythrophlœum, in which the pressure sometimes remains high for many seconds, or even for a minute or more, after the heart has finally ceased to beat (Fig. 89).

Investigation of the Action of Drugs on the Arterioles.

The arterioles become contracted by the action of the involuntary muscular fibre contained in their walls; they dilate partly by their own elasticity and partly by the pressure of fluid within them.

The capillaries also appear to have the power of contraction. Both arterioles and capillaries are induced to contract by the effect upon them of the nerves which pass to them from vaso-motor centres. The blood-vessels may also dilate actively from irritation of vaso-inhibitory nerves. The exact mode of action of these nerves is not ascertained; they are generally looked upon as entirely separate from vaso-motor, but it seems not improbable that here also the difference between vaso-motor and vaso-inhibitory nerves is a mere question of relation, and some nerves produce contraction and dilatation according to the point where they are stimulated. Thus Dastre and Morat have found that the cervical sympathetic, which produces contraction of the vessels in the rabbit's ear when irritated between the ear and the first thoracic ganglion, causes dilatation instead of constriction when it is irritated at a point below the ganglion, in which case the stimulus has to pass through the ganglion before it reaches the ear.

In considering the action of drugs on the vessels, we have, therefore, to examine—

1. Their direct effect upon—
   A. The contractile walls of the vessels themselves with their
      a, muscular fibres,
      b, motor ganglia;

[1] John Hunter's works, edited by Palmer, 1837, vol. iii. p. 91.

B. Nerve-fibres
a, vaso-motor,
b, vaso-dilating;

C. Nerve-centres
a, vaso-motor,
b, vaso-dilating.

2. Their reflex effect on the nerve-centres just mentioned.

There are two **modes of estimating the contraction** of the arterioles: 1st, by direct observation and measurement under the microscope; 2nd, by ascertaining the quantity of blood or other fluid which will pass through them in a given time.

Each of these methods may be used in several ways, according as we wish to ascertain the action of a drug—1st, on the contractile walls of the vessels alone; 2nd, on the walls together with the vascular nerves but without the nerve-centres; and 3rd, on the vessels in connection with the nerve-centres.

The method of direct observation of the arterioles may be practised in either frogs or mammals.

The part of the **frog** usually selected is the web, the mesentery, the mylo-hyoid muscle, the tongue, or the lung. The parts usually observed in **mammals** are the wing of the bat and the ear of the rabbit.[1]

In observing the effect of various conditions on the lung, it is necessary to inflate it. This is easily done by means of a small cannula with a bulging end which is tied into the larynx. Over the other end is slipped a small piece of india-rubber tubing, and by clamping this after the lung has been inflated, the escape of air is prevented.

An apparatus for this purpose is described by Holmgren.[2] The accompanying engraving (Fig. 92) shows one which I used in 1870 for the purpose of investigating the action of heat and cold upon the lung.[3]

By means of the india-rubber ball I directed upon the lung a stream of air which was previously passed either through hot water or through iced water. The pulmonary capillaries, when treated in this way, contract under the influence of cold by one-third of their diameter. McKendrick, Coats, and Newman, in an investigation on the action of anæsthetics on the pulmonary circulation, found that chloroform, ethidene, and ether, all stop the pulmonary circulation, the action of chloroform being greatest and that of ether least.[4]

In observing the **effects** of drugs on the **vessels** alone, it is necessary to destroy the influence of the nerve-centres over them.

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[1] For observing the vessels of the rabbit's ear one of Brücke's lenses is very convenient. It resembles a telescope in its construction, but has a very short focus.

[2] Ludwig's *Festgabe*.

[3] *British Medical Journal*, Feb. 13, 1875, p. 204.

[4] *Ibid.* Dec. 18, 1880.

This is usually done in a frog by destroying the brain and spinal cord. In the rabbit's ear it is done by dividing as far as possible all the nerves going to one ear, then injecting the drug into the general circulation and comparing its effect upon the two ears.

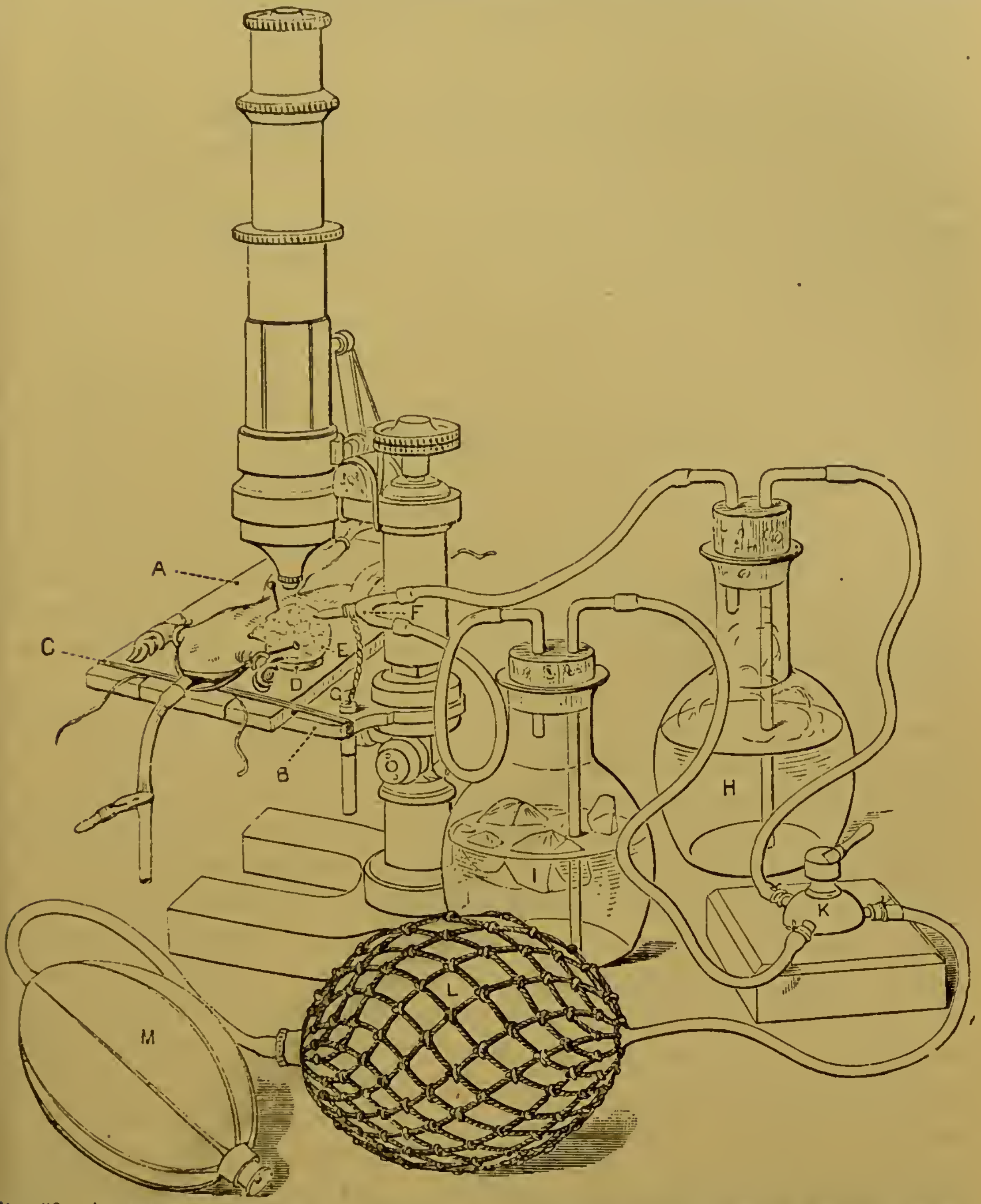

FIG. 92.—Apparatus for ascertaining the effect of heat and cold on the vessels of the frog's lungs. A, a piece of cork to which the frog is fastened, is laid on B, the stage of a microscope, and attached by an india-rubber strap, C. D is a small ring of cork covered with a thin circle of glass. E is the inflated frog's lung. F is a tube by which a current of air can be directed on the frog's lung. It is held in position by a piece of wire, G, which can be bent to any position. I is a flask containing ice and water. H, a flask containing hot water. K is a three-way stopcock, by which a current of air may be sent from the spray-producer, L and M, through either I or H at will, and thus cold or hot air may be applied alternately to the lung.

It is evident, however, that such experiments are not free from fallacy, because in them the circulation is dependent on the condition of the heart as well as that of the vessels; and both of these may be affected by the drug.

A better plan, therefore, is to obviate this fallacy by keeping

up the circulation artificially, either in the body of the frog, or in the ear of the rabbit.

A method of **maintaining artificial circulation** in the rabbit's ear while the calibre of the vessels is being measured was invented by Ludwig, and described by me in the *British Medical Journal*, 1871.

In the frog artificial circulation is kept up by putting a cannula into the aorta, and another into the vena cava or abdominal vein after destruction of the brain and spinal cord. The aortic cannula is connected with two funnels or bottles, such as are used for artificial circulation through the intestine (p. 382). These contain either a saline solution or a mixture of saline solution with defibrinated blood. To one of them the drug is added. The circulation can be rendered quicker or slower at will, by increasing the pressure under which the fluid flows into the aorta. A suitable part of the frog is then put under the microscope, and the vessels measured while unpoisoned blood flows through them. The poisoned blood is then allowed to circulate under exactly the same conditions of pressure and the vessels are measured again. By this method of observation Gaskell ascertained that very dilute alkalies cause great contraction of the vessels, so as sometimes almost entirely to occlude them and arrest any flow of blood through them. Dilute acids counteract this effect and cause the vessels again to dilate.

Cash and I have observed that, in addition to this action, dilute **acids** have a tendency to increase the exudation of fluid from the vessels and produce **œdema** of surrounding tissues.

In many experiments which have been made on the action of drugs on the blood-vessels by direct microscopic measurement of their size, before and after the application of the drug, no account has been taken of the effect which the application of the drug may produce by its local irritating action on the nerves or tissues of the part to which it is applied, and by its reflex action through the nerves, quite independently of any special action which it may have on the vessels. Thus, irritation by the application of alcohol, either alone or as a solvent in tinctures, or by a strong saline solution, has an effect similar to that of simple irritation by pressure or scratching, and usually causes temporary contraction, followed by dilatation of the capillaries. This contraction may be more or less prolonged, according to the strength of the irritant which is applied. Unless these conditions are taken into account, observations on the effect of drugs applied locally to the web, mesentery, or tongue, are very unsatisfactory and generally worthless.

Perhaps a somewhat better result may be obtained by injecting the drug into the lymph-sac of a frog, and then observing the web. But here also we have the same difficulty, because the sensory nerves of the lymph-sac being irritated, reflex stimulation

of the vaso-motor centre and consequent contraction of the vessels may be induced.

Method of Measurement by Rate of Flow.—Another method of ascertaining the effect of drugs on the vessels is to measure the amount which flows out of them in a given time. This method may be employed either in the frog or in the higher animals. The method of employing it in the frog is to destroy the brain and spinal cord, and tie one cannula into the heart or aortic bulb, and another into the inferior vena cava. The aortic cannula is connected with a reservoir containing saline solution, or defibrinated blood, which can be made to pass into the aorta and circulate through the vessels at any desired pressure by simply raising or lowering the reservoir; the fluid flows out through the cannula in the vena cava, and the quantity is registered upon a revolving cylinder.

By this method Cash and I have found that potassium chloride, contrary to our expectation, causes great contraction of the vessels; that barium and calcium and strontium do so also, but to a less extent. The instrument used for this purpose consists of a light lever, one end of which is depressed each time that a drop falls upon it. An electric circuit is thus broken, and the fall of each drop is readily recorded by means of an electro-magnetic marker; at the same time the pressure under which the circulation is going on is also recorded by means of a manometer. Slowing of the flow indicates of course contraction of the vessels, and acceleration indicates dilatation of the vessels.

The general results of our experiments with several metallic salts are shown in the accompanying table. Most of the drugs experimented on cause contraction of the blood-vessels, but we are unable at present to arrange them in the exact order of their strength of action.

Lithium causes slight contraction.
Potassium (very dilute solutions) causes dilatation.
  Ditto (solutions of $\frac{1}{4000}$) causes contraction.
Barium causes rapid contraction.
Calcium ,, gradual ,,
Strontium ,, gradual ,,
Magnesium ,, slight ,,
Aluminium (much diluted) has no effect. 1 per cent. needed to produce any effect.

Iron causes slow contraction.
Copper ,, powerful ,,
Zinc ,, ,, ,,
Tin ,, ,, ,,
Cadmium ,, slight ,,
Nickel ,, ,, ,,
Cobalt ,, ,, ,,
Platinum ,, powerful ,, but none is produced by solutions weaker than $\frac{1}{5000}$.

In experiments made by such methods as that just described we reduce the problem of the action of drugs on the blood-vessels to a very simple form, although we have still to distinguish whether the drug acts directly on the contractile walls of the blood-vessel or on the nervous elements contained in them. There is at present no means of absolutely separating those two factors, but it is probable that the nerves die sooner than the

muscular fibres, and that if the experiments are carried on for some time the effect of the drug is chiefly, if not entirely, exerted upon the muscular fibres. This is probably the explanation of the different effects of chloral on the vessels of the kidney observed by Ludwig and Mosso (p. 283).

In experiments on the flow of blood through the vessels of warm-blooded animals, the circulation is kept up in much the same way as in the frog. The blood may be used cold, or may be kept at the temperature of the body. The cannula is usually inserted either into the artery supplying an organ such as the kidney, or supplying a single muscle, or it may be put into the descending aorta, so that the blood passes through the whole of both lower extremities. The flow is measured by the rate at which the blood issues from the corresponding vein.

This method we owe to Ludwig, who, along with his pupil Mosso, made a number of experiments on the circulation through the kidney. The conclusions arrived at were:—that venous blood causes contraction, and oxygenated blood, dilatation of the vessels; but the dilatation which richly oxygenated blood, circulating after venous blood, causes in the vessels is only temporary, and they soon return to their normal calibre. Mosso's experiments have been repeated by Severini, who used the lung instead of the kidneys. He finds that the alternate circulation of oxygenated and of venous blood acts in the manner described by Mosso, but that when oxygenated blood is passed through steadily the vessels contract and the flow through them is diminished; venous blood, on the contrary, when circulated for a length of time causes the vessels to dilate and the flow through them to increase. The action of venous blood upon the arterioles appears indeed to be similar to its action upon other tissues. A small or moderate quantity of carbonic acid acts as a stimulus and causes contraction, but great interference with the natural process of oxidation produces paralysis.

Nicotine, in the proportion of 1 in 10,000, causes contraction of the vessels; but this is also temporary. One per cent., on the contrary, immediately causes dilatation.

Atropine has a very powerful action; but this differs completely according to the dose. One part in 100,000 causes temporary contraction of the vessels, which soon passes off. One in 10,000 causes contraction, which, instead of returning simply to the normal, passes into dilatation, and then returns to the normal. One in 5,000 has a similar action, but instead of the dilatation passing away, and the vessels returning to their normal size, the dilatation persists, and the kidney soon dies.

Chloral causes the vessels to contract and then to dilate; but besides this it has a peculiar action, either increasing rhythmical contraction and dilatation of the vessels, when such movements are already present, or inducing them when they are absent. It

only acts upon the vessels when the blood contains oxygen; and when the blood is saturated with carbonic acid, it has no action on them at all. Its action is also altered by the condition of the kidney. When this organ has been kept for twenty-four hours in a cool place, its vessels still retain their irritability; but small doses of chloral, instead of causing contraction followed by dilatation, only produce contraction, and a much larger dose is required to produce dilatation. This alteration is due to a change in the vessels—either in their muscular walls, or more probably in the ends of the vaso-motor nerves—and not to any change in the blood; for it occurs when serum instead of blood is passed through the kidneys. When the kidney is dead, chloral mixed with the blood, instead of increasing the rapidity of the current as in the living organ, or leaving it unaltered, as one would expect, greatly diminishes it. Chloral also alters the effect of artificial stimulation of the kidney. Faradaic currents or induction-shocks do not seem to affect the normal vessels, but constant currents cause dilatation, which continues while the currents are passing and diminishes after they cease. When chloral is added to the circulating blood, however, the vessels contract during the passage of the current instead of dilating, and dilate slightly after the current has ceased. When the chloral has acted so far upon the vessels as to dilate them greatly, the constant current causes no alteration while it is passing, but, after it ceases, dilatation increases still further.

Action of Drugs on Vaso-motor and Vaso-dilating Nerves.

The effect which irritation of the vascular nerves produces in the living body is also altered by the action of drugs. This effect is of two kinds—vaso-motor or vaso-contracting, and vaso-dilating. Fibres, having these two different actions on the vessels of a part, appear frequently to run together in the same nerve-trunk, so that sometimes we get dilatation, at other times contraction of the vessels on irritation of a nerve, and not unfrequently we get contraction followed by dilatation. Such fibres, however, are not contained in equal proportions in different nerve-trunks. The splanchnics, for example, chiefly contain vaso-motor fibres, so that irritation of these nerves causes great contraction of the vessels in the intestine, and a rise of blood-pressure. The motor nerves of the muscles, on the contrary, appear to contain chiefly vaso-inhibitory fibres, so that stimulation of the nerve causes dilatation of the vessels in the muscle to which it is distributed. Similarly, irritation of nerves distributed to glands usually causes dilatation of the vessels in them. The chorda tympani affords a marked example of this, though the same thing is noticed also in the case of the sweat-glands in the foot on irritation of the sciatic nerve.

Most of these vaso-motor or vaso-inhibitory nerves can be stimulated reflexly by irritation of a sensory nerve, as well as directly by irritants applied to the nerves themselves.

We are not acquainted with many drugs which have the power of paralysing the ends of the vaso-motor nerves in the vessels apart from an action upon the contractile walls of the vessels, or the central nervous system. Arsenic, however, appears to be a drug of this kind, and in acute poisoning by arsenic Böhm has observed that neither irritation of the splanchnic nerves nor of the medulla raises the pressure in the way it usually does. From this effect Böhm concludes that the motor nerves contained in the splanchnics are paralysed, but some other observers have not obtained similar results. Hay has found that potash has a similar action. The method is not free from fallacy, for it is obvious that if the vessels in the intestine should happen to be already contracted either from the effect of a drug upon them or from any other cause, neither stimulation of the splanchnics nor of the medulla can have any further effect upon them or on the blood-pressure through them. For when the vessels of the intestine are contracted the blood pours into the veins from the aortic system, through the arterioles and capillaries of the voluntary muscles, and these are only to a very slight extent under the control of the vaso-motor centre in the medulla. Irritation of it will therefore have little effect on the general blood-pressure when the arterioles of the intestine are already contracted, and irritation of the splanchnics is also prevented from having much effect.

It seems probable that curare and poisons which, like it, not only paralyse the ends of the motor nerves, but also the ends of the vagus in the heart, also paralyse vaso-motor nerves, though larger doses are required for this purpose.

Vaso-dilating fibres appear also to be paralysed by curare, for irritation of the motor nerve of a muscle does not cause dilatation [1] of the vessels in a muscle of an animal deeply poisoned by curare. Stimulation of the spinal cord produces contraction of the vessels of the penis instead of erection in an animal poisoned by curare,[2] and stimulation of the chorda tympani does not cause the same amount of dilatation in a poisoned as in a non-poisoned animal, even when the dose of curare is small.[3] Small doses of curare, however, and even large doses of opium, do not appear to paralyse the vaso-dilating nerves of muscles.

In some experiments which I made on the chorda tympani, I got a different result from the usual one in an animal thoroughly under the influence of opium. The vessels appeared to contract

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[1] Gaskell, *Journ. of Physiol.* 1878–9, vol. i. p. 273.
[2] Eckhard, *Beiträge*, vol. vii. p. 67.
[3] V. Frey, Ludwig's *Arbeiten*, 1876, p. 98.

instead of dilating on irritation of the chorda tympani, so that instead of the blood gushing out of the vein, it flowed slowly, drop by drop.

Action of other parts on the Blood-pressure.—It has already been mentioned that the blood-pressure rises during muscular exertion, as, for example, during the struggles of an animal. The cause of this has not been definitely ascertained, but it is probably, to a great extent, due to the flow of blood through the muscles being mechanically obstructed by the contraction of the muscular fibres and to a more rapid action of the heart.

The flow of blood through those organs which consist of involuntary muscles, e.g. the intestine, may be also obstructed.

When physostigmine is given to an animal, the blood-pressure is sometimes noticed to rise considerably, and this rise of pressure was at first attributed to contraction of the arterioles. According to Von Bezold and Götz, however, this is due, to a great extent, not to the contraction of the arterioles themselves, but to mechanical obstruction of the intestinal vessels by the tetanic contraction of the muscular walls of the intestine.[1]

Reflex Contraction of Vessels.—Experiments on the outflow of blood from divided vessels, while the nervous system is intact, are sometimes made on frogs for the purpose of ascertaining the direct effect of drugs on the arterioles themselves; but this method is faulty, for the alterations consequent on the injection of the drug may be simply due to its local irritant action producing reflex contraction.

Such experiments are usually made by snipping off the toe of a frog, then injecting the drug into the lymph-sac and observing how many drops of blood exude in a given time from the toe before and after the injection.

It is obvious that if no change occur in the heart, and the openings of the divided vessels do not become obstructed by clots or otherwise, these experiments may give some indication regarding the contraction of the vessels; but the results are not trustworthy unless we can ascertain the condition of the heart. A modification of this experiment enables us to some extent to do this. The end of a toe on *each* foot having been snipped off, the nerve in *one* leg is divided and then the drug is injected into the lymph-sac. If it be then found that the flow of blood from the foot, whose vaso-motor supply has been destroyed by division of the nerve, continues unchanged or is even increased after the injection of the drug, while that from the other foot is diminished, we may conclude that the diminution is due to contraction of the vessels caused by the injection of the drug.

But it is incorrect to assume, as has sometimes been done,

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[1] *Centralblatt f. d. med. Wiss.*, April 6, 1867, p. 234.

that this contraction is due to any specific action of the drug, either upon the muscular walls of the blood-vessels or upon the vaso-motor centre. There is here a fallacy similar to that already mentioned in respect to direct observation of the size of blood-vessels. Any irritation of a sensory nerve by pinching, scratching, heat, &c., may cause reflex stimulation of the vaso-motor centre and produce contraction of the vessels, and injection of strong saline solutions into the lymph-sac, having a local irritant action, will produce a similar effect.

As an example of this fallacy we may mention certain experiments with bromide of potassium. In such experiments it was found that injections into the lymph-sac were followed by contraction of the vessels of the toes, so that much less blood flowed after the injection. When the sciatic nerve was divided on one side the flow was not lessened but rather increased in the corresponding foot, at the same time that it was much diminished on the other side where the nerve was intact. This result clearly shows that after the injection the vessels in one foot contracted, and that this contraction was due to the effect of the injection on the vaso-motor centre, inasmuch as it did not occur in the foot whose vessels had been withdrawn from the influence of this centre by division of the nerves. From this fact the conclusion has been drawn that bromide of potassium has a special power of contracting blood-vessels generally, and on this conclusion theories of its action upon the nervous system have been based. Such theories, however, rest on a very untrustworthy foundation; for though contraction of the vessels no doubt followed the injection of a strong solution of bromide into the lymph-sac, this contraction was probably not at all due to any specific action of the bromide, but only to the reflex stimulation of the vaso-motor centre caused by its local irritant action at the place of application. If introduced in a dilute solution into the mouth instead of in a concentrated form into the lymph-sac, this local irritant action would be absent and probably no contraction of the blood-vessels would be produced.

Action of Drugs on Reflex Contraction of Vessels.—Irritation of a sensory nerve usually produces reflex stimulation of the vaso-motor centre and consequent contraction of the vessels and rise in the blood-pressure both in the frog and higher animals. The chief vaso-motor centre is situated in the medulla oblongata, but it is probable that there are many subsidiary centres throughout the body. It is probable also that these vary in strength and in the amount of independent action they possess in different animals. When the influence of the chief vaso-motor centre upon the body is destroyed by section of the spinal cord just below the medulla, the vessels dilate and the blood-pressure falls greatly. This is, however, not always the case, for in some dogs I have noticed that after section of the

medulla, the blood-pressure remained so high that I was under the impression that the cord had been imperfectly divided, yet after death examination of the cord showed that section was complete.

The vaso-motor centre is paralysed by numerous drugs, especially in the final stages of their action, so that its ordinary tonic action is destroyed and the blood-pressure falls greatly. Its action of responding to a reflex stimulation is also abolished, and irritation of a sensory nerve no longer raises the pressure. The tonic and reflex action of the centre do not always appear to be effected *pari passu*,—chloral, for example, appearing to have a greater power to diminish its reflex action than its tone, so that stimulation of a sensory nerve has little or no effect even when the blood-pressure has not as yet fallen very low. Sometimes, indeed, an opposite effect to the usual one may be produced and the blood-pressure be lowered still further instead of raised by the stimulation. Alcohol also paralyses very markedly both the reflex power and the direct excitability of the vaso-motor centre, so that neither stimulation of a sensory nerve, nor even stimulation of the centre of suffocation, will raise the blood-pressure.[1] Both the normal tone and the reflex excitability of the vaso-motor centre are greatly increased by strychnine. The general blood-pressure greatly rises after the injection of this drug, and the effect of irritation of a sensory nerve upon it is increased. It has already been mentioned that in ordinary circumstances the subsidiary vaso-motor centres in the cord when separated from the medulla cannot of themselves maintain the blood-pressure. After the injection of strychnine, however, their action is so much increased that they may keep the blood-pressure at a high average and may also cause it to rise on irritation of a sensory nerve.

Comparative Effect of the Heart and Vessels on Blood-pressure in different Animals.—The influence of these two factors—the heart and the vessels—on the blood-pressure varies in different animals, and under different conditions; and a number of the discrepancies observed by various investigators are probably due to this circumstance. Thus, in dogs the effect of the heart is very considerable, and when its beats are quickened by division of the vagi the pressure rises; in rabbits, on the other hand, the heart, instead of working well under its power as in the dog, beats very rapidly in the normal condition, and when the vagi are divided the pressure does not rise much, although when they are stimulated the pressure falls both in the dog and in the rabbit. This different action of the vagus in the dog and rabbit is well seen when these animals are poisoned by atropine. This drug completely destroys the inhibitory action of the vagus on

[1] Dogiel, *Pflüger's Archiv*, 1874, Bd. viii.

the heart; and when the inhibitory power is completely removed we find that only a slight increase in the number of beats takes place in the rabbit, the pulse-rate rising one quarter: for example, perhaps from 100 to 125. In the dog, on the contrary, the pulse-rate will rise to three times, or even four times, what it was before.

In man the effect of the vagus on the heart is intermediate between that of the rabbit and dog: so that if the normal pulse is between 70 and 80 in the minute, it rises to between 140 and 180 when the vagus is paralysed by atropine (Von Bezold).

This difference between the effect of the vagus on the heart alters the effect of drugs on the blood-pressure in different animals.

The difference in the action of drugs on the dog and rabbit is well shown in the case of nitrite of amyl. If this be given by inhalation to a rabbit, the blood-pressure falls immediately and rapidly. If given to a dog the fall may be very slight, at least if a small quantity only is used. On counting the pulse in the dog we discover at once the cause of the apparent difference in the action of the drug on the two animals. Before inhalation the pulse of the dog was slow, but after inhalation its pulse became almost as quick as that of the rabbit. In both animals the nitrite causes dilatation of the vessels, but in the dog the heart begins to beat so much more rapidly than usual that it maintains the blood-pressure nearly at the normal, notwithstanding this dilatation; while the heart of the rabbit beats so quickly, normally, that it cannot maintain the pressure by increased rate of pulsation. If the vagi be cut in the dog, so that the heart beats rapidly like that of the rabbit before inhalation, the nitrite causes as sudden a fall as in the rabbit.[1]

The numerous factors which have to be taken into consideration in regard to the blood-pressure, the action and the interaction of different parts of the body upon one another, render it by no means easy to understand the effect of drugs on the circulation. The differences which we find in the action of drugs on different animals seem at first to make matters still worse; but it is through these differences of action that we learn the exact mode in which the various factors of the circulation are affected by the drug.

There are at least two other factors which must be borne in mind in relation to the difference between rabbits and dogs: these are (1) the much greater sensitiveness of the inhibitory nerves of the heart to reflex stimulation from the nose as well as to stimulation by venous blood, in the rabbit than in the dog; and (2) the proportionately much greater length of the intestinal tube in the rabbit, which causes the vessels of the intestines, on

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[1] Lauder Brunton, *Journ. of Anat. and Physiol.*, Nov. 1870, p. 95.

account of their number, to exercise a greater action on the blood-pressure in it than in the dog. Thus, in the rabbit, a slightly irritating vapour will cause the animal to close its nostrils; and almost immediately the vagus will be excited and the heart will stop. This stoppage is probably chiefly due to reflex action on the heart through the nasal nerves, though it may be partly due to accumulation of carbonic acid in the blood. When the spinal cord is divided in the rabbit just below the medulla, the pressure sinks enormously: in the dog it also sinks, but not to the same extent; and in some cases it sinks so little that it is almost impossible to believe that the cord has been divided, until examination after death shows that the section has really been completed. This effect may be partially due to the less power which the dilatation of the intestinal vessels, consequent upon the section, has in the dog. It may also, however, be partly due to greater development of extra-cranial vaso-motor centres in the spinal cord and elsewhere, than in the rabbit.

Influence of Nerves on Blood-pressure.—Both the quickness of the heart's beat and the contraction of the arteries are regulated by the **nervous system**; and it is generally by their action on it that drugs alter the blood-pressure, though it must be constantly borne in mind that they may also do so by acting directly on the **muscular walls** of the heart and arteries themselves. The parts of the nervous system chiefly concerned in regulating the circulation are:

I. The **motor cardiac ganglia** which lie in the walls of the heart, and are under ordinary circumstances the cause of its rhythmical action.

II. **Inhibitory nerves,** which render the heart's action slow, and, if irritated very strongly, may stop its beating altogether, and produce quiescence in **diastole.** The inhibitory fibres have their origin or roots in the medulla, and proceed in the vagi to the heart. In probably all the higher animals they are normally in more or less constant action. In men and dogs they maintain a well-marked action; and, after they are cut or paralysed, the heart beats in the dog three or four times as quickly, and in man twice as quickly, as before. In rabbits and cats they act less, and their division only makes the heart go one-half or one-fourth faster. In frogs they are not in constant action, so that their section does not usually quicken the beats of the heart in these animals.

A drug may **irritate** them, and render the heart's action slow—

1. By acting **directly** on (*a*) their roots in the medulla, (*b*) their ends in the heart;

2. **Indirectly,** through its action on other parts, producing (*a*) increased blood-pressure, or (*b*) accumulation of carbonic

acid in the blood, both of which act as irritants to the vagus roots;

3. **Reflexly,** through irritation of sensory nerves, e.g. irritation of the intestines; of the sympathetic nerve; of the depressor; or of certain afferent fibres in the vagus. Reflex irritation is only likely to be caused by drugs having a powerful local action.

Drugs may also paralyse the inhibitory, or the ends of inhibitory, nerves in the heart, and thus quicken the heart.

Inhibitory ganglia have been supposed to exist in the heart, and certain drugs, such as muscarine, are supposed to slow its pulsations by their action on these ganglia. They have been supposed to be distinct from the ends of the vagus (p. 313), although generally when the ends of inhibitory nerves in the heart are spoken of, the inhibitory ganglia are included in the term.

III. **Quickening Nerves.**—These belong to the sympathetic system. They have their origin in the brain or medulla, pass down through the cervical part of the spinal cord to the last cervical and first dorsal ganglion (which in many animals are united), and thence through the third branch of the ganglion to the heart. Quickening fibres are said by some to run also in the cervical part of the sympathetic cord. In the frog the accelerating fibres pass from the spinal cord in the anterior root of the third nerve into the ganglion on the trunks of the glosso-pharyngeal and vagus and thence in the vagus trunk to the heart (Gaskell). Unlike the inhibitory nerves, the quickening nerves are not normally in constant action in mammals.

The accelerating centres may be stimulated—

1. By the **direct** action of drugs upon them.

2. **Indirectly** by the drugs producing a diminution in the blood-pressure. Such a diminution acts as a stimulus to them.

FIG. 93.—Diagram to show the supposed relation of motor ganglia in the heart to accelerating fibres. A, accelerating fibres proceeding from the cerebro-spinal or sympathetic nervous systems to the motor ganglia of the heart. G, motor ganglion. *a*, accelerating fibres passing from the endocardium to the motor ganglion. *m*, motor fibres to the cardiac muscle. H, the cardiac muscle. [For the sake of simplicity in this diagram all hypotheses regarding separate motor and accelerating ganglia have been disregarded.]

It is probable that accelerating fibres also pass to the cardiac ganglia from the endocardium, for irritation of the interior of the heart, either mechanically or by the injection of irritating drugs

into it, causes acceleration. The supposed relationship of the various accelerating fibres to the cardiac ganglia is shown in the accompanying figure (Fig. 93).

IV. **Vaso-motor Nerves**, which cause the smaller arteries, and probably also the capillaries, to contract. These belong to the sympathetic system; and the most important of them are contained in the splanchnics, which when stimulated produce contraction of the intestinal vessels. As these vessels can, under certain circumstances, hold all the blood in the body, the influence of the splanchnics over the blood-pressure is very great; and division of them can lower it, or stimulation of them increase it, very much. The intestine being much longer in herbivora than carnivora, the splanchnics have a greater influence over the blood-pressure in the former. The chief centre of the whole vaso-motor system seems to be in the medulla oblongata; and it is generally in constant action, keeping up a certain amount of contraction or tone in the vessels. There are also, however, subsidiary centres in the spinal cord, and possibly also in the ganglia of the sympathetic system.

The activity of the **vaso-motor centres** may be increased (cf. p. 276), and the vessels made to contract—

1. By **direct** irritation of these centres.

2. By **reflex** irritation through (*a*) the cervical sympathetic, (*b*) the vagus, when the brain is intact, and the animal not narcotised, (*c*) sensory nerves, including the splanchnics themselves. When the medulla is separated from the rest of the body by dividing the spinal cord at the atlas, it can, of course, no longer exert any influence over the vessels; they consequently become dilated throughout the whole body, and the blood-pressure usually sinks very low. If the lower end of the divided cord be then irritated, the vaso-motor nerves which pass through it from the medulla to the body are stimulated, and the blood-pressure rises.

It is probable that the **peripheral ends** of the vaso-motor nerves in the vessels themselves may be either stimulated or paralysed by the action of drugs conveyed to them by the general circulation.

V. **Depressor nerves.**—Irritation of these nerves is conducted to the vaso-motor centres, and acts on them in such a way as to cause a reflex dilatation of the small vessels, either (1) **generally** throughout the whole body, or (2) **locally** in one particular part of it.

1. The chief nerve which causes dilatation, especially affecting the intestinal vessels, is one which runs from the heart to the medulla, and is called, from its power of diminishing blood-pressure, the depressor nerve. Its fibres seem to be included in the vagus in the dog; but in the rabbit it generally runs separate from the heart to the level of the thyroid cartilage; here it

divides into two so-called roots, one root going to the superior laryngeal, and the other to the vagus nerve. These are generally called roots, though, as the nerve conveys impressions from the heart to the brain, they are, physiologically, really branches. There seem to be also depressor fibres in the vagus itself; but the vagus contains fibres of many kinds, and, among others, some which cause reflex contraction of the vessels and rise of blood-pressure—hence called pressor-fibres. The depressor-fibres of the vagus seem to act on the vaso-motor system through the medulla itself, while the pressor-fibres affect it through a centre in the brain, so that, when the brain is perfect, irritation of the central end of the vagus causes increased contraction of the vessels and raised blood-pressure; but, when the brain is removed or its functions abolished by opium, it causes dilatation of vessels and diminished pressure.

2. When a sensory nerve is irritated, the action of the vaso-motor centre is suspended in the part supplied by the nerve, and in those which immediately adjoin it, so that their vessels become dilated, while at the same time contraction of the vessels in other parts of the body is produced. The blood-pressure is thus increased generally, and produces in the locally dilated vessels a very rapid stream of blood. This fact was first discovered, and its therapeutics indicated, by Ludwig and Lovèn.

The causes of alteration in blood-pressure as well as in the pulse-rate, will perhaps be more easily seen from the table on the next page.

Action of the Heart on Blood-pressure.—I have already mentioned that we can to a certain extent ascertain whether a rise or fall in blood-pressure is due to the heart or arterioles, by comparing the pressure-curve with the pulse-curve (p. 271 *et seq.*). If they run parallel the effect may be attributed in great measure to the heart.

But the effect of the heart on the blood-pressure is not so simple as that of the arterioles. In the case of the arterioles we have to consider only the rate at which the blood will flow through them when they are more or less contracted; but in the case of the heart we have to consider not only the rapidity of its pulsations, but the amount of blood which is sent into the arterial system at each beat. We judge of the amount of blood chiefly by the extent to which the blood-pressure oscillates with each pulsation. A large quantity of blood will, as a rule, cause an extensive, and a small quantity only a slight oscillation. When the heart is beating slowly, so that it has time to fill completely during each diastole, the oscillations are large, and when it is beating quickly the oscillations are small.

It is evident that although quick pulsations tend to raise the blood-pressure, they only do so up to a certain point, as beyond that, the heart does not get properly filled, and so sends but little blood into the aorta at each

Causes of Alterations in Blood-pressure and Pulse-rate.

Blood-pressure may be diminished	By slow action of the heart	Irritation, or increased excitability of vagus roots	Directly, by the action of the drug on them. Indirectly, by increased blood-pressure. „ by accumulation of CO_2 in the blood. Reflexly, by irritation of some afferent nerve.
		Irritation, or increased excitability of vagus ends in the heart	
		Paralysis of sympathetic ends in the heart (?)	
		Weakness of the heart	Paralysis of the cardiac ganglia. Paralysis of the cardiac muscular fibres.
	By smallness in the amount of blood sent into the heart at each systole	Imperfect systole of the heart. Imperfect diastole of heart. Contraction of the pulmonary vessels. Great dilatation of the venous system.	
	By dilatation of the small arteries	Paralysis of the vaso-motor centre	Directly, by the action of the drug. Reflexly, through the depressor. Reflexly, through vagus and sensory nerves, when brain is removed or animal poisoned by opium.
		„ „ „ peripheral ends	
		„ „ „ fibres	In operations by division of the cord or of the splanchnics.
		Paralysis of the muscular coat of the arterial walls.	
Blood-pressure may be increased	By quick action of the heart	Paralysis of vagus roots. Paralysis of vagus ends in heart.	
		Stimulation of sympathetic roots	Directly, by action of drug. Indirectly, by lowered blood-pressure.
		Stimulation of sympathetic ends in heart (?)	
		Stimulation of the cardiac ganglia	Directly. Reflexly, by stimulation of the sensory nerves of the endocardium. Indirectly, by causing increased temperature of body.
	By larger amount of blood at each beat	More perfect diastole and systole.	
	By contraction of the small arteries	Irritation of vaso-motor centre	Directly, by action of drug on it. Indirectly, by accumulation of CO_2 in the blood. Reflexly, through the cervical sympathetic. Reflexly, through the vagus, when the brain is present, and the animal is not narcotised. Reflexly, through sensory nerves.
		„ „ peripheral terminations. Direct irritation of muscular coat of vessels.	
		„ „ „ vaso-motor fibres	In operations by irritation of the peripheral ends of the divided spinal cord or splanchnics.

Stimulation of nerve-fibres of course frequently occurs in experiments from the application of a faradaic current to the trunk of a nerve, but it probably never occurs from the action of drugs introduced into the general circulation.

beat. But the heart may sometimes be imperfectly filled even when it is beating slowly; this has been shown to occur in the case of the frog by Goltz. When a blow or two is struck on the intestines the veins dilate and the blood accumulates in them, so that the heart, which is also stopped at first, receives no blood when it does begin to beat again. It can therefore send none into the aorta, and the circulation remains completely arrested, although the heart is beating.

If the pulmonary capillaries also are contracted the left ventricle will receive little blood, and so will send little blood into the arteries, although the right ventricle may be much distended. This appears to occur during poisoning with muscarine, which causes the lungs to become blanched,[1] the right ventricle distended, and the left ventricle and the arterial system empty: so that little blood flows from a wound.[2]

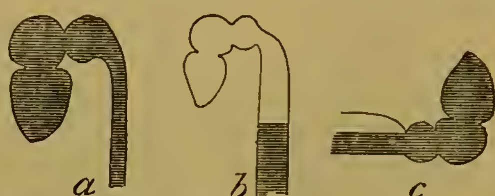

FIG. 94.—For description *vide* p. 263.

It is difficult, however, to estimate precisely the quantity of blood sent into the arteries at each beat, and its relation to the rapidity of the pulse, so as to ascertain directly how much the rise or fall of blood-pressure is due to the heart; and therefore this is sometimes estimated indirectly by ascertaining first how much of the effect of the drug on the blood-pressure is due to the arterioles, and then attributing to the heart what is not accounted for by their action.

Sometimes also we may get useful information by compressing the abdominal aorta as near the diaphragm as possible before and after injection. We thus diminish so greatly the number of capillary outlets by which the blood may flow from the arteries into the veins that we greatly lessen, though we do not quite destroy, the effect of the arterioles on the blood-pressure. We can thus estimate more precisely the action of the heart upon it.

Section of the spinal cord below the medulla oblongata, by destroying the effect of the vaso-motor centre upon the vessels, also aids us in estimating the action of the heart.

Another method of ascertaining what share in alterations of the circulation locally is due to the heart and arterioles respectively, consists in the combined use of the manometer and Ludwig's stromuhr or Marey's hæmodromometer. The manometer shows the general blood-pressure while the hæmodromometer shows the rate of circulation in the particular artery experimented upon. If the rate of flow increases while the blood-pressure remains constant or sinks, it is evident that the arterioles of the particular vascular district to which the artery is distributed have become dilated. If, on the other hand, the rate of circulation diminishes while the pressure remains constant or rises, it is clear that the arterioles have become contracted.

This method is only capable of being applied to large arteries such as the carotid or femoral. By placing the stromuhr in the femoral artery, Dogiel and Kowalewsky found that during suffocation the rapidity of the blood-flow diminished while the pressure rose, showing that the peripheral vessels were contracted.[3]

[1] Lauder Brunton, *Brit. Med. Journ.*, Nov. 14, 1874.
[2] Schmiedeberg and Koppe, *Das Muscarin*, p. 57.
[3] *Pflüger's Archiv*, 1870, p. 489.

By the use of the stromuhr, Dogiel[1] has found that the rapidity of the flow of blood in the carotid is first increased and then diminished by alcohol, the greatest diminution occurring during complete narcosis.

Effect of Drugs on the Pulse-rate.—The pulse-rate, i.e. the rapidity of the heart's beats, is chiefly regulated by the inhibitory fibres of the vagus, although it is affected also by accelerating fibres. In the frog the latter, excepting those which pass to the motor ganglia of the heart from the endocardium, also run mainly in the vagus, which is really the vago-sympathetic (Gaskell). In the higher animals they run chiefly through sympathetic channels, though to a slight extent also in the vagus.

If we find that the administration of a drug quickens the pulse, we next try to discover the mode in which it has done so. A glance at the table (p. 293) will show that there are several ways in which acceleration may occur, though the most important is either paralysis of the vagus or, at least, cessation of its action. The usual stimulus to the vagus-roots in the medulla which calls the nerve into action is the pressure of blood within the medulla; when this is high the vagus-roots are stimulated, and the pulse becomes slow; when the pressure is low, the stimulus is removed, and the pulse again becomes quick. Alterations in the blood-pressure will therefore alter the pulse, and drugs which affect the arterioles may quicken or slow the pulse-rate without any marked action of their own on the heart or vagus. This has already been mentioned when speaking of nitrite of amyl, which, by lowering the blood-pressure, and thus lessening the normal stimulus to the vagus-roots, greatly quickens the heart in the dog (p. 288).

In order to ascertain whether irritation of the vagus has been caused reflexly or not, we may divide the nerves through which we may expect the reflex to have occurred, or we may abolish their action on the medulla to a great extent by the use of large doses of chloral.

Action of Drugs on the Cardio-inhibitory Functions of the Vagus.

When speaking in the following pages of the inhibitory action of the vagus on the heart I mean its power to affect the rhythm of the heart so as to render its pulsations slow or stop them entirely, and I do not include under the term inhibition, the power which the vagus also possesses of enfeebling the cardiac contractions, unless when this is expressly stated.

We distinguish between (*a*) stimulation of the vagus-roots by any cause whatever, and (*b*) stimulation of its ends in the heart[2]

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[1] *Pflüger's Archiv*, 1874, vol. viii., p. 606.

[2] We use the term vagus-ends here for the sake of convenient distinction between the central cardio-inhibitory systems in the medulla oblongata and the peripheral one in the heart. A fuller explanation of the peripheral cardio-inhibitory apparatus will be given further on.

by dividing both vagi. Sometimes we inject the drug first, and see whether any slowing of the heart which it has produced disappears on section, or we may divide them before injecting the drug, and see whether any change, either in the way of slowing or acceleration, occurs after the injection. If the effect of a drug in slowing the heart is removed by dividing the vagi, we conclude that its action has been exerted on the vagus-roots: if it should still persist after their division, we conclude that it has acted on the vagus-ends in the heart or on the heart itself.

Thus aconitine,[1] veratrine,[2] erythrophlœum,[3] and probably all members of the digitalis[4] group stimulate the vagus-roots, so that the slowing of the pulse they produce is much lessened or completely abolished by section of the vagi, and takes place to a much less extent when the vagi are divided before the injection. That the slowing does not always completely disappear after section of the vagi, or is not always completely prevented by their previous section, is due to the fact that most of these drugs have also an action either on the ends of the vagus in the heart, or on the nervous mechanism or muscular fibre of the heart itself. Nicotine resembles the substances already mentioned in so far that the slowing which it would otherwise produce is somewhat lessened by section of the vagi, but only to a slight extent, its action being chiefly exerted on the peripheral cardio-inhibitory system.[5] Physostigmine chiefly affects the heart itself, and so the slowing of the pulse it causes is not abolished by section of the vagi.[6]

Reflex Stimulation of the Vagus.—The vagus-centre may be also stimulated reflexly, and slowing or stoppage of the heart produced by irritation of sensory nerves. This stimulation occurs most readily through the nasal, dental, or other branches of the fifth nerve, the nucleus of which is closely connected with that of the vagus, or through the sensory branches of the vagus itself, but it may also be induced through almost any sensory, and some sympathetic nerves, if the stimulus be strong.

The vagus-centre in rabbits appears to be very readily stimulated through the nasal nerves, for the application of any strong vapour such as ammonia or chloroform to the nose not only induces closure of the nostrils and stoppage of respiration, but also complete arrest of the heart's pulsations. It appears also to be very sensitive to venous blood. Stoppage of the heart may occur in man from irritation of a sensory nerve, even under

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[1] Vide *Dissertation on Aconitine under Böhm's direction*, by C. Ewers, Dorpat, 1873.

[2] Von Bezold and Hirt, *Würzburger physiol. Untersuch.* i. p. 103.

[3] Brunton and Pye, *Phil. Trans.*, 1877, p. 627.

[4] Traube and others.

[5] Traube, *Med. Centralztg.* 1862 and 1863, No. 9; *Centralblatt f. d. med. Wiss.* 1863, pp. 111 and 159; Rosenthal, *Centralblatt f. d. med. Wiss.*, 1863, p. 737.

[6] Fraser, *Trans. of Roy. Soc. of Edinburgh*, 1867, reprint, p. 39; for other literature *vide* Harnack, *Arch. f. exp. Path. u. Pharm.*, Bd. v. p. 446.

chloroform anæsthesia, and indeed I believe that in excision of the eyeball the heart usually misses one beat at the moment the nerves are divided.

In dogs, stoppage of the heart and death may occur from irritation of the stomach, even when complete anæsthesia has been produced by chloroform. Some years ago, when making a gastric fistula in a dog, the animal, which was in a state of profound anæsthesia from chloroform, suddenly died when the stomach was laid hold of with forceps. This occurred in a second case just as the cannula was being introduced. On mentioning the subject to Professor Schiff, he informed me that he had had several cases of a similar sort when using chloroform as an anæsthetic, but had none after he began to use ether instead. I found also on using ether that no further death occurred.

Causes of Quickened Pulse.—If, instead of causing a slowness of the pulse, the drug produces **quickening**, it may be due to paralysis of the vagi, to stimulation of the accelerating nerves, or to direct action on the heart itself. We ascertain whether the drug has paralysed the ends of the vagus in the heart by injecting it, and then irritating the vagi in the neck by a faradaic current. If we find that we are no longer able to slow or stop the heart by stimulation of the vagi, we conclude that the drug has paralysed these nerves. This action is well-marked in the case of atropine.

Action of Drugs on Vagus-roots.—We may wish to know, however, what the action of the drug has been on the vagus-roots, and it is evident that if the ends in the heart are paralysed, no action on the vagus-centre could alter the pulsations of the heart any more than nervous stimuli proceeding from the cord could move the legs of an animal poisoned by curare. Nor can we separate the vagus-centre from the heart by ligature of the vessels so readily as one isolates the frog's leg. It can be done no doubt by tying the carotid and vertebral arteries and keeping up an artificial stream of blood through the head. Instead of this, however, the simpler method is generally adopted of injecting the drug to be tested into the carotid artery, so that it will reach the vagus-centre before it gets to the heart, instead of injecting it as usual into the subcutaneous tissue or veins, whence it will be carried to the heart before it can reach the vagus-centre.

By experimenting in this way it is shown that atropine stimulates the vagus-roots so that when injected into the carotid it causes slowing of the heart's action. When it has passed through the cerebral vessels, and returns with the blood to the heart it paralyses the ends of the vagus in the heart, and therefore the pulse again becomes very rapid, notwithstanding the continued stimulation of the vagus-roots.

We cannot always conclude with certainty that a drug has excited the vagus-roots merely because it has caused the pulse to become slower and has had no action after the vagi have been divided, for it is possible that the terminations of the vagus in the heart may be rendered more sensitive than usual by a drug, so that they may respond to a slighter stimulus than usual or with greater energy to a normal stimulus. Such an action appears to be exerted by physostigmine, which in a certain stage of poisoning renders the vagus more excitable, so that when irritated in the neck by a faradaic current a slighter stimulus suffices to stop the heart after the administration of the drug than before.

Action on Accelerating Nerves.—We ascertain whether a drug has a stimulating action on the accelerating nerves of the heart by cutting both vagi and then injecting the drug. If it quickens the heart still further, we assume that it does so by stimulation of the accelerating nerves. This experiment, however, does not enable us to decide whether the stimulation has affected the accelerating nerves passing to the cardiac ganglia from the central nervous system or those passing from the endocardium.

Stimulating Effect of Asphyxial Blood on the Medulla.—In order to prevent fallacies arising from stimulation of the vagus-roots by an asphyxial condition of the blood due to the action of the drug upon respiration, it is usual to maintain artificial respiration through a cannula placed in the trachea. This acts perfectly well in some cases, but if the drug should cause violent convulsive actions it may prevent the movements of the thorax occurring regularly, and therefore it is sometimes necessary to paralyse them by means of curare.

Moreover, it must be remembered that prolonged stoppage of the heart itself will allow the blood in the medulla to become venous and will thus irritate the vagus-roots. Prolonged arrest of the heart, therefore, tends by this action to prolong it still further, and functional inactivity tends to pass into death. This mechanism would render every intermission of the pulse very dangerous were it not that the same venous condition of the blood which stimulates the vagus-roots stimulates also the vaso-motor centre and the respiratory centre. The vaso-motor centre by contracting the arterioles maintains the blood-pressure during the prolonged diastole, and excitation of the respiratory centre tends to restore the arterial character of the blood. The venous condition of the blood also stimulates accelerating centres in the medulla (Dastre and Morat).

Stimulation of the Heart by increased Blood-pressure.—It has already been mentioned that increased blood-pressure usually renders the beats of the heart slower by the stimulating action it exerts on the vagus-roots. When the vagi are divided, however, its effect is usually quite different, and a rise in blood-pressure after division of the vagi renders the pulse quicker instead of slower, at least generally. An opposite result has been found by Marey in the heart of the tortoise, where increased pressure rendered the beats slower. The reason of the difference observed between the mammalian heart and that of the tortoise is probably due to the different development of the nervous and muscular structures. The tortoise heart acts more like a single simple muscle, and the more resistance it has to overcome the more slowly does it work.

In the mammalian heart the increased pressure appears to stimulate the nerves, so that the more resistance it has to overcome the more quickly does it work—that is, if the vagi have been cut. The sensibility of the nervous system in the heart to increased pressure appears to be diminished by atropine, for Schiff[1] has found that a quantity of this poison slightly larger than will dilate the pupil lessens the sensibility of the heart to changes in blood-pressure so much that the pressure may be first increased to three times the normal and then diminished to one-half, or even one-third, without any change in the pulse-rate being produced.

[1] *La Nazione*, 1872, No. 235.

Such an observation suggests that atropine would be useful in lessening pain or palpitation of the heart in persons with high blood-pressure or suffering from the effects of cardiac strain consequent on violent muscular exertion. I have tried it in such cases sometimes with apparently great benefit, at other times with little result. The cases of failure may, however, have been due to the remedy not being pushed far enough, as in them the pupil was not markedly dilated.

Palpitation.—In what I have just said regarding the effect of blood-pressure on the heart I have spoken of the total work, including in it both the rapidity of pulsation and the amount of work done by each beat. This is, perhaps, fair enough; but at the same time we must not forget that there is a distinction between the total amount of work done and the nature of the individual contraction, either in the heart of tortoises or mammals, or in voluntary muscles. Both voluntary muscles and the heart tend to contract rapidly if they have little resistance to overcome. In patients suffering from anæmia and debility, where the blood-pressure is low and the resistance to the ventricular contractions is consequently small, they are apt to take place with great quickness, giving rise to a short flapping first sound and a short but unsustained apex-beat, while the patient complains of much palpitation. In such cases increased blood-pressure will tend to lessen the palpitation, and digitalis, which contracts the vessels, will be useful; iron also is serviceable by increasing the nutrition of the circulatory apparatus of the body generally. The low blood-pressure, however, while it increases the tendency to palpitation, is not the only factor, and is usually accompanied by a tendency to disturbance of the cardiac innervation, which is to be met by sedatives such as the bromides, or by remedies directed to the stomach or other organs from which the disturbing stimulus may proceed.

The Heart of the Frog.

This is a very convenient object on which to study the action of drugs. Their effects upon it are somewhat, though not absolutely, the same as their effects on the mammalian heart; and the frog's heart being simpler in its construction it is easier to analyse the exact mode in which drugs act upon it. The frog's heart consists of three chambers, one ventricle and two auricles. But in addition to these, there is what might almost be called a fourth chamber, the venous sinus or sac into which the venæ cavæ open.

There are three venæ cavæ, two superior and one inferior, which open into the venous sinus.

The venous sinus itself opens into the right auricle, the opening being covered during the auricular systole by a small fold which acts as a valve.

The left auricle receives the pulmonary veins and discharges into the single ventricle the arterial blood which enters it from them, while the right auricle does the same with the venous blood it receives from the sinus.

The septum between the auricles ends inferiorly in two triangular flaps, which act as valves between the auricles and ventricle.

From the ventricle issues the common aorta, or aortic bulb, which has at its origin from the ventricle a spiral valve to prevent the return of the blood. The two auricles beat together, and the aortic bulb and ventricle usually beat together, though the bulb is capable of independent pulsation.

FIG. 95.—Diagram of the frog's heart.

The usual rhythm is the following: first the venous sinus, next the auricles, then the ventricle and bulb.

The pulsations of the venous sinus and ventricle alternate with those of the auricle. The heart continues to pulsate rhythmically after it has been completely removed from the body, so that the motor power of rhythmical contraction is evidently contained within itself. Its rhythm is, however, regulated by the vagi nerves. These pass along behind the two superior cavæ to the junction of the venous sinus with the auricle. At this spot, or

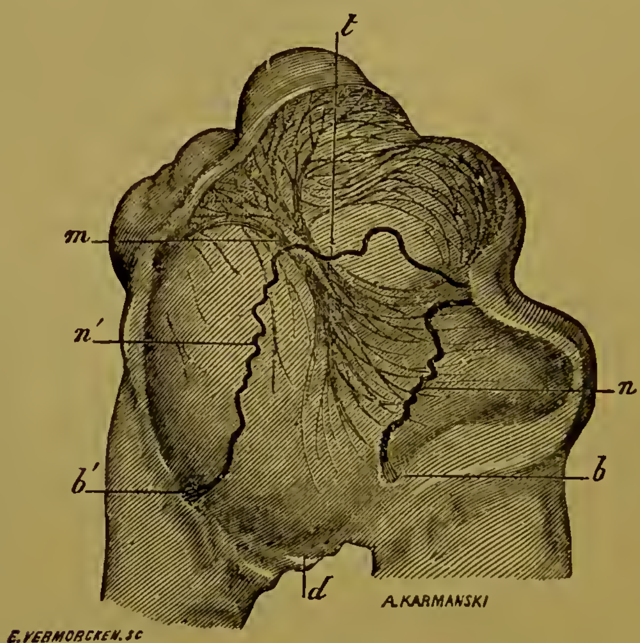


FIG. 96.—View of the auricular septum in the frog (seen from the left side). The nerves are stained with osmic acid. *n* is the posterior, and *n'* the anterior cardiac nerve; *t* is a horizontal portion of thel atter nerve; *b* is the posterior, and *b'* the anterior auriculo-ventricular ganglion; *m* is a projecting muscular fold. [This figure is taken by the kind permission of my friend, M. Ranvier, from his *Leçons d'Anatomie générale*, Année 1877–78, 'Appareils nerveux terminaux,' t. 6, p. 79.]

just over the auricles, between the superior cavæ and the pulmonary veins, they anastomose to form a single or double ganglion, or a plexus containing ganglionic cells, sometimes known as Remak's ganglion. From hence two nerves pass down in the auricular septum, to the base of the ventricle, where they end in two ganglia, known as Bidder's ganglia (Fig. 95). These are situated at the junction of the wall of the ventricle with the two valvular flaps in which the septum ends. They are connected with one another by fibres which run transversely, nearly in a line with the auriculo-ventricular groove.

The posterior or dorsal nerve comes chiefly from the left vagus; and the anterior or ventral from the right vagus.

Both of these nerves grow thicker as they pass down towards Bidder's

ganglia from the presence in them of numerous ganglionic cells; they also send off several branches to the auricle.

The ventricle itself has not been shown to contain either nerve-fibres or ganglionic cells, excepting just at its base, where Bidder's ganglia already mentioned are situated, and where branches from them proceed to the ventricle.

Action of Drugs on the Heart of the Frog.

The effect of drugs may be observed by simply destroying the brain, exposing the heart, and either injecting the drug subcutaneously, or into the dorsal lymph-sac, or even laying it upon the heart itself. Changes in the rate of the pulse and in the mode of contraction of the different cavities of the heart are thus readily observed. By exposure and irritation of the vagi the effect of drugs upon their action can also be observed. Even when completely excised, the heart of the frog continues to pulsate for a length of time, and the action of heat, cold, and poisons upon it can be readily demonstrated. A simple apparatus for this purpose is shown in Fig. 97.

FIG. 97.—Instrument for showing the action of heat and cold and of poisons on the frog's heart. It consists of a piece of tin plate or glass three or four inches long and two or three wide, at one end of which an ordinary cork cut square is fastened with sealing-wax in such a manner that it projects half an inch or more beyond the edge of the plate. This serves as a support to a little wooden lever about three inches long, a quarter of an inch broad, and one-eighth of an inch thick. A pin is passed through a hole in the centre of this lever, and runs into the cork, so that the lever swings freely about upon it as on a pivot. The easiest way of making a hole of the proper size is simply to heat the pin red hot, and then to burn a hole in the lever with it. To prevent the lever from sliding along the pin, a minute piece of cardboard is put at each side of it, and oiled to prevent friction. A long, fine bonnet-straw, or section of one, is then fastened by sealing-wax to one end of the lever, and to the other end of the straw a round piece of white paper, cut to the size of a shilling or half-crown, according to convenience, is also fixed by a drop of sealing-wax. The pin, which acts as a pivot, should be just sufficiently beyond the edge of the plate to allow the lever to move freely, and the lever itself should lie flat upon the plate. Its weight, too, increased as it is by the straw and paper flag, would now be too great for the heart to lift, and so it must be counterpoised. This is readily done by clasping a pair of bulldog forceps on the other end. By altering the position of the forceps the weight of the lever can be regulated with great nicety. If the forceps are drawn back as at *c*, the flag is more than counterbalanced, and does not rest on the heart at all, while the position *a* brings the centre of gravity of the forceps in front of the pivot, and increases the pressure of the lever on the heart. The isolated frog's heart is laid under the lever near the pivot, and as it beats the lever oscillates upwards and downwards. When used for demonstrating the action of poisons the wooden lever should be covered with sealing-wax, so as to allow every particle of the poison to be washed off it, and thus prevent any portion from being left behind and interfering with a future experiment. By attaching a small point to the end of the straw in place of the paper flag, tracings may be taken upon smoked paper fixed on a revolving cylinder.

The fact that heat accelerates and cold retards the pulsations of the heart is one of fundamental importance, both in regard to a right understanding of the quick pulse, which is one of the most prominent symptoms of fever, and to a correct knowledge of the proper treatment to apply when the heart's action is failing.

It may be shown with the apparatus just described by placing a piece of ice under the tin plate. The pulsations will become slower and slower, and if the room be not too warm the heart may stand completely still in diastole. On removing the ice from the plate the pulsations of the heart become quicker. If a spirit-lamp

be now held at some distance below it the heart beats quicker and quicker as the heat increases, until at last it stands still in heat-tetanus. On again cooling it by the ice, its pulsations recommence.

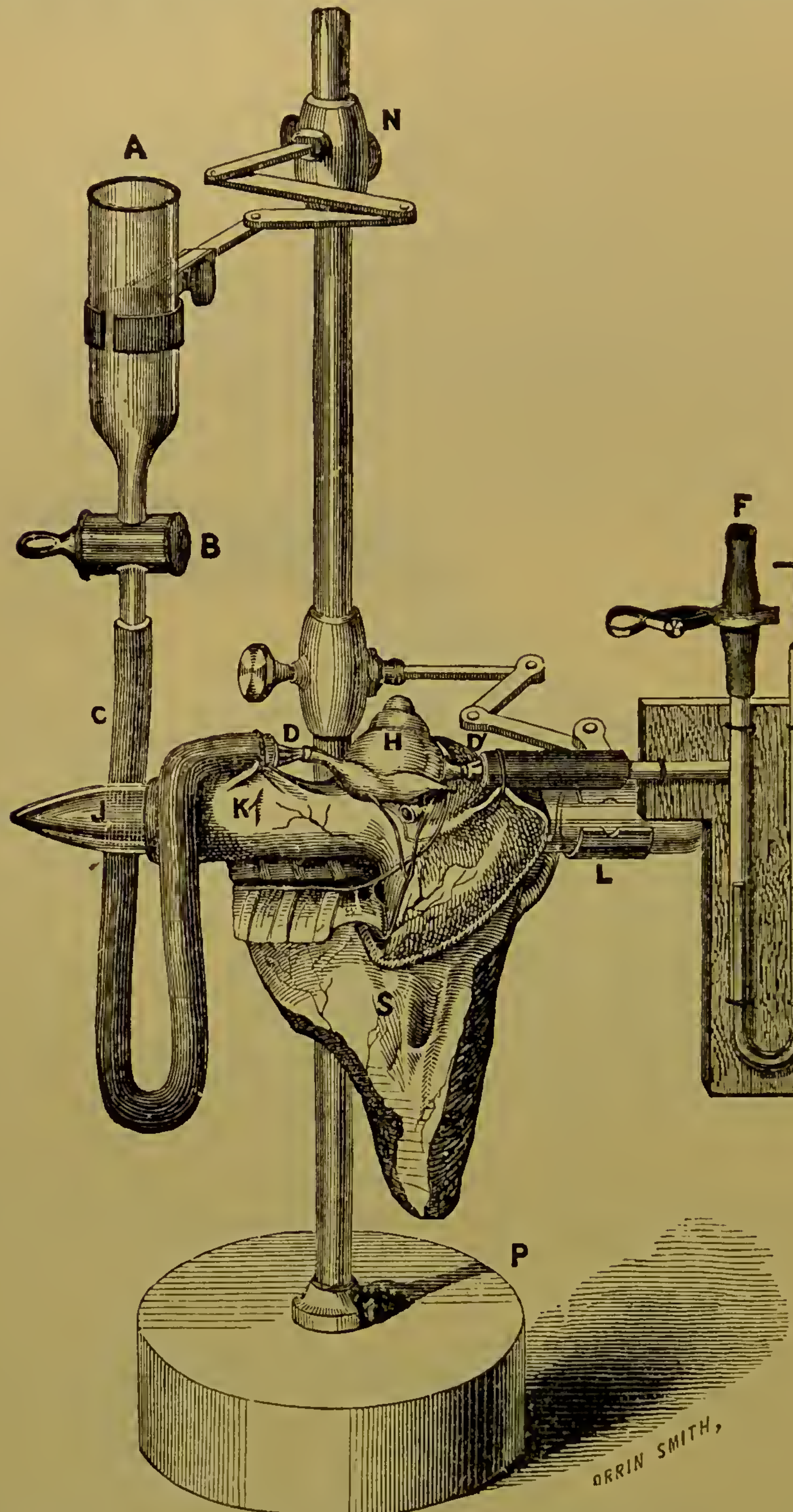


FIG. 98.—Ludwig and Coats' frog-heart apparatus. A is a reservoir for serum. B, a stopcock to regulate the supply to the heart. C, a piece of caoutchouc tubing connecting A and D. D, a glass cannula in the vena cava inferior. D′, another in the aorta. E, a manometer. F, a piece of tubing closed by a clip, to allow of the escape of serum. G, a fine pen, floating on the mercury in E. H, the frog's heart. J, a sealed glass tube passed through the œsophagus, K. and firmly held by a holder, L. N, a second holder to support A. P, a stand with upright rod. S, a flap of skin to cover the heart and prevent drying. The vagus nerve is seen passing to the heart.

At first they are quick, but they gradually become slower and slower. On again applying the spirit-lamp they become quicker, and by raising the temperature sufficiently the heat-tetanus is converted into heat-rigor. In this condition no application of cold has the slightest effect in restoring pulsation.

Not only the effects of heat and cold, but the effect of separating the venous sinus or the auricles from the ventricle can readily be shown with this apparatus, as well as the action of various poisons. The best for the purpose of class demonstration is muscarine. A drop of saline solution containing a little of the alkaloid being placed on the heart, it ceases to beat entirely. If a drop of atropine solution be now added the beats recommence. I have seen them do so on one occasion after they had entirely ceased for four hours.

For the purpose of observing alterations in the strength of the cardiac pulsations as well as their rhythm, a convenient piece of apparatus is the one devised by Ludwig and used under his directions by Coats (Fig. 98).

One objection to this apparatus as shown in the engraving is, that the blood does not circulate freely through the heart, but this can be overcome by closing the tube at F only partially instead of completely, and according to the amount of closure the pressure under which the heart works may be regulated. Or the tube F may be lengthened and made to empty itself into the reservoir A. The pressure under which the heart works may be regulated by the height at which the tube is allowed to discharge.

Another apparatus is that used by Williams in his researches on digitalin (Fig. 99).[1] It consists of a Y-shaped cannula whose stem is divided by a

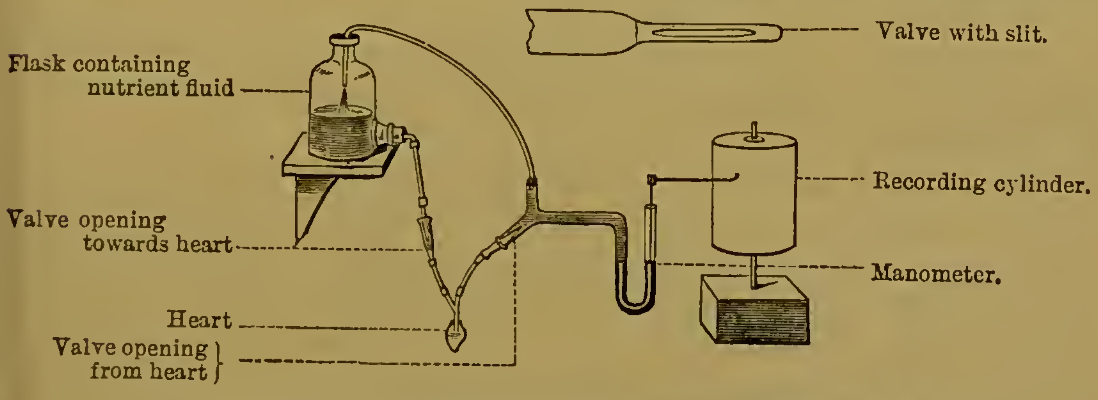


FIG. 99.—Diagram of Williams's apparatus for investigating the action of drugs on the heart of the frog.

longitudinal septum into two halves, each of which is continuous with the fork on its own side. The stem is inserted through the aorta into the ventricle of the heart, which is kept moist by being dipped in a vessel containing serum or a dilute saline solution. One fork of the Y is connected with a flask containing blood-serum or other nutritive fluid, and the other with a manometer. By means of valves these fluids are made to flow only in one direction. These valves consist of a piece of glass tubing with a slit on one side; over this slit is loosely tied a piece of thin membrane (gold-beater's skin) which covers about three-quarters of the circumference of the tube. This membrane allows fluid to pass readily out of the tube from within outwards, but not from without inwards, any external pressure causing the membrane to become tightly applied to the slit and to close it.

[1] *Arch. f. exp. Path. u. Pharm.*, Bd. xiii. p. 1.

A very useful form of apparatus for investigating the action of drugs on the frog's heart and on the effect of the vagus upon it is made by combining the valves in Williams's apparatus with the apparatus of Ludwig and Coats.[1]

The **apex** (as the lower two-thirds of the ventricle is commonly called) contains, as has been mentioned, **no nerves**, and when separated from the rest, either by cutting or by tight ligature, usually lies perfectly quiet without contracting. When irritated by a single induced shock, it answers by a single contraction, just like any other muscular fibre.

But though the muscular fibres contained in the apex cease to contract rhythmically, when the nervous stimulus usually supplied by Bidder's ganglia is removed, they still retain a tendency to rhythmical contraction; and when subjected to a constant stimulus of another kind they again commence to pulsate. This is seen when the apex is stimulated by supplying it with oxygenated blood through a cannula under pressure (the pressure supplying the necessary stimulus), or by passing through it a constant or interrupted current, or by adding a trace of delphinine to the nutritive fluid with which it is supplied. This phenomenon is similar to that which occurs in the bells of medusæ already described (p. 110), which cease to contract rhythmically when their marginal ganglia are removed, but recommence when an additional stimulus is applied to the bell itself, by putting it into acidulated water.

A curious point has been made out by Bowditch regarding the excitability of the heart-apex. It has already been mentioned that the amount of contraction of voluntary muscle varies with the intensity of the stimulus, and that this is also the case with the reflex contraction produced by irritation of sensory nerves. The apex when fed with serum usually stands still for a long time before it begins to beat, but when in this condition may be made to contract by the application of an induction shock. The difference between the reaction of an ordinary striated muscle and of the apex to such a shock is, that the heart, instead of responding by a strong or weak contraction to a strong or weak stimulus, either does not contract at all or contracts with as much force as it can exert. The weakest stimulus which will act at all and the strongest have thus exactly the same action, or, in other words, a minimum is also a maximum stimulus. This condition does not correspond to that which obtains in the normal striated muscle when stimulated either directly or reflexly. We find, however, a corresponding condition in the reflex contraction of the muscle produced by stimulation of sensory nerves in an animal poisoned by strychnine (p. 181). We noted, however, in discussing the action of strychnine on the

[1] Harnack and Hoffmann, *Arch. f. exp. Path. u. Pharm.*, Bd. xvii. p. 159.

spinal cord, that, just after exhaustion had occurred from a spasm, strong and weak stimuli produced strong and weak contractions in the muscle. A somewhat similar condition appears to occur in the heart, for Mays has noticed that, when the apex is supplied with blood which has stood three or four days instead of with fresh blood, strong and weak stimuli produce strong and weak contractions.[1]

It is obvious that, although the contractions of voluntary muscle on reflex stimulation may be analogous to the contractions of the apex, yet, in the former case, the alterations occur in the nervous centres, while in the apex the changes occur in the muscular substance.

Action of Drugs on the Muscular Substance of the Heart.

Since the lower two-thirds of the ventricle or **apex**, as it is usually termed, contains no nerves, it forms a convenient object for ascertaining the action of drugs upon the muscular substance of the heart itself and has been much used for this purpose.

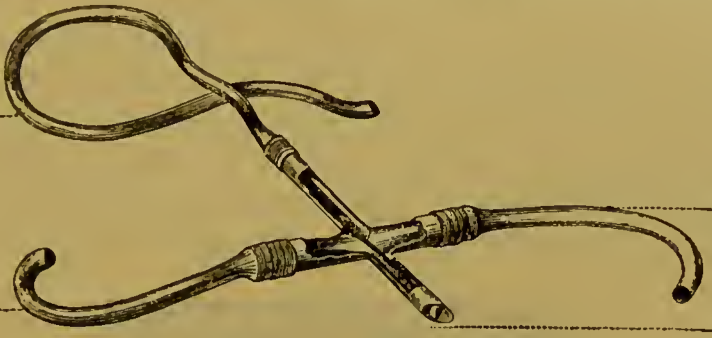


FIG. 100.—Perfusion cannula, with the anterior part removed so as to show the septum.

The apparatus usually employed (Fig. 100) consists of a small cannula introduced into the ventricle, which is attached to it by a ligature tightly tied round it at the junction of its upper third with its lower two-thirds. The interior of the cannula is divided into two by a septum which runs longitudinally, and the one half is connected with a flask containing the nutritive fluid with which it is to be supplied, and the other with a small mercurial manometer provided with a float to register its oscillations upon a revolving cylinder.

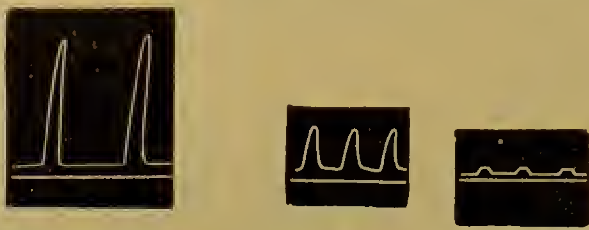
At first the nutritive fluid is supplied pure to the apex, and after a normal tracing has been obtained the substance to be investigated is added to it.

When **saline solution**, a ·65 per cent. solution of NaCl, is employed, the apex usually stops in diastole for a period varying from a few minutes to an hour and a half. It then begins to pulsate (Fig. 101, *a*), getting gradually weaker and weaker (Fig. 101, *b* and *c*), and finally stops in diastole. When the heart is in this condition its pulsations may be restored by the addition

[1] *Separat-Abdk. a. d. Verhandl. d. physiol. Gesellsch. zu Berlin*, Jan. 12, 1883.

to the chloride of sodium solution of 1 to 10 per cent. of blood, or of serum, or of a solution of the ashes of serum.

Minute quantities of several poisons such as delphinine or quinine, or a mixture of atropine and muscarine, also restore the



a b c

FIG. 101.—After Ringer. Tracings showing the effect of simple NaCl solution in weakening the pulsations of the apex of the frog's heart. The tracing *a* was taken soon after the blood was replaced by NaCl solution; *b*, after a longer period; and *c* after a still longer time.

rhythmical pulsations after they have ceased in a heart-apex supplied with NaCl solution. A minute quantity of Na_2CO_3 or ·005 per cent. of NaHO restores or increases the beats for a time [1]; afterwards the pulsations become again weaker and the heart stops a second time, but it stops in systole and not in diastole.

Ringer has made the remarkable discovery that when the saline solution is made with ordinary tap-water the beats become prolonged, but the addition of a trace of potash causes them at once to assume their normal character, and a frog's heart may be kept beating for hours together with saline solution made in this way and containing a trace of potash, although the saline solution never does this when made with distilled water. The

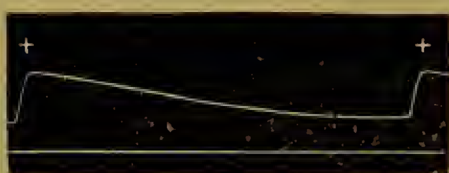


FIG. 102.—After Ringer. Shows the effect produced upon the beat of the frog's heart fed with NaCl solution by the addition of a trace of calcium chloride. The beats in this case are induced by an induction shock.

addition of a minute trace of calcium salt to distilled water produces the same effect as tap-water—the contractions become larger and longer (Fig. 102). When potash is then added, the length of the contractions becomes diminished to the normal without their strength becoming affected, and thus a pure saline solution made with distilled water and with the addition of minute traces of calcium and potassium will keep the heart beating perfectly for hours together.

Dilute **alkalies** added to the saline solution have been shown by Gaskell to cause a tonic contraction of the muscular fibre of the apex, so that it may gradually cease to beat. This contraction may occur whether the apex is pulsating or not. If it

[1] Gaule, *Archiv f. Anat. u. Phys.*, 1878, p. 295.

remains at rest, a manometer connected with it simply shows a gradual rise in the mercury until the contraction of the apex is complete. If it is beating, the duration of full contraction at each systole becomes longer, and relaxation during diastole less complete, until no diastolic relaxation occurs and the ventricle remains perfectly still in a condition of complete contraction.

Dilute acids have an opposite action to dilute alkalies, and when very dilute acid, e.g. lactic acid, is mixed with the saline solution, it produces a condition of complete relaxation.

Instead of increasing the duration of the systole like alkalies, acids first shorten it and then render it less and less powerful, until contractions cease altogether and the ventricle remains at rest in diastole.

Dilute acids and alkalies counteract each other's effects on the heart, so that after the beats have been very much lowered in force by acids, an alkali will first restore it to its original condition, and then produce its own characteristic effect. The subsequent application of an acid will undo the effect of the alkali, again weakening the beats and again producing dilatation instead of contraction.[1]

The three alkalies, potash, soda, and ammonia, have all a somewhat similar tendency to increase the tonic contraction of the ventricle. When large doses are given they tend to paralyse the muscle, so that it again dilates after a period of tonic contraction. The paralysing action of potash is much more powerful, and manifests itself much sooner than that of the other two.

The excitability of the muscular fibre is also altered by alkalies. Soda and ammonia increase it, so that a faradaic stimulus applied to the ventricle has much more effect after the application of soda and ammonia than before. Potash has a different effect and diminishes the excitability of the ventricle, although sometimes the diminution may be preceded by a stage of increased excitability.[2]

A number of poisons act on the muscular fibre of the ventricle like alkalies, others act like acids.

Antiarine, digitalin, helleborin, veratrine, physostigmine, barium, and probably all the substances belonging to the digitalin group, act like alkalies.

Muscarine[3] acts like an acid, and so apparently do also pilocarpine,[4] saponine,[5] and apomorphine.

Neutral double salts of copper, chloral, iodal, and other members of the chloral group,[6] are probably to be classed along

[1] Gaskell, *Journ. of Physiol.*, vol. iii. p. 48.
[2] Ringer, *Ibid.*, vol. iii. p. 193.
[3] Gaskell, *Journ. of Physiol.*, vol. iii. p. 61.
[4] *Ibid.*, *op. cit.*
[5] Schmiedeberg, *Ludwig's Festgabe*. p. 127.
[6] Harnack, *Archiv f. exp. Path. u. Pharm.*, Bd. xvii. p. 185.

with salts of potassium, first exciting and then paralysing the cardiac muscle.

In classifying cardiac poisons, when we say that some act like acids and others like alkalies, it must be borne in mind that the action though similar is not identical. Although the actions may be generally like one another, they may vary very considerably even in kind, and they certainly vary enormously in degree. Thus the action of barium and veratrine may be very similar, but veratrine is much the more powerful. We find a similar condition in other structures. Thus iodide of ammonium and curarine both paralyse the ends of motor nerves, but an enormously larger amount of the former is required to produce the effect.

That there is considerable similarity in kind, however, between the action of the vegetable alkaloids and inorganic salts is shown by the fact that the action of veratrine may be neutralised by potassium chloride.[1]

The irritability of the heart is preserved for very different lengths of time in different gases. Thus Castell[2] found that the frog's heart continued to beat in oxygen for 12 hours, in nitrogen for 1 hour, in hydrogen for 1¼ hour, in carbonic acid for 10 minutes, in nitrous oxide for 5 or 6 minutes, in carbonic oxide for 40 minutes, and in chlorine for 2 minutes.

Differences between the Heart-Apex and the Heart.

When the heart is tied on to a cannula in the same way as the apex, by a ligature round the auricles or even the sinus, so that, instead of containing no ganglia at all, it contains either Bidder's or Bidder's and Remak's ganglia, it also remains motion-

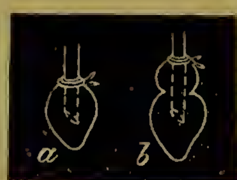


FIG. 103.—Diagram to show the difference in the mode of experimenting with the heart and with the apex alone. In *a* the apex alone is attached to the cannula. In *b* the heart, consisting of ventricle and auricles, or of the venous sinus also, is attached to the cannula.

less in the same way as the apex when supplied with chloride of sodium solution, but its rhythmical power is restored by the addition of defibrinated blood, of serum, of solution of the ashes of serum, by a trace of Na_2CO_3, or still better by the addition of ·005 per cent. of NaHO and a trace of peptone or serum-albumin.

When supplied with pure serum, it does not beat regularly, but its pulsations occur in groups separated by long intervals (Fig. 104).[3] When a little hæmoglobin or blood is added to the

[1] Ringer, *Practitioner*, vol. xxx. p. 17.
[2] Hermann's *Handb. d. Phys.*, iv. 1, p. 357.
[3] Luciani, *Ludwig's Arbeiten*, 1872, p. 120.

serum, this grouping disappears, and the pulsations become regular.[1]

When the heart has been supplied with hæmoglobin or blood and is beating regularly, the addition of a little veratrine causes

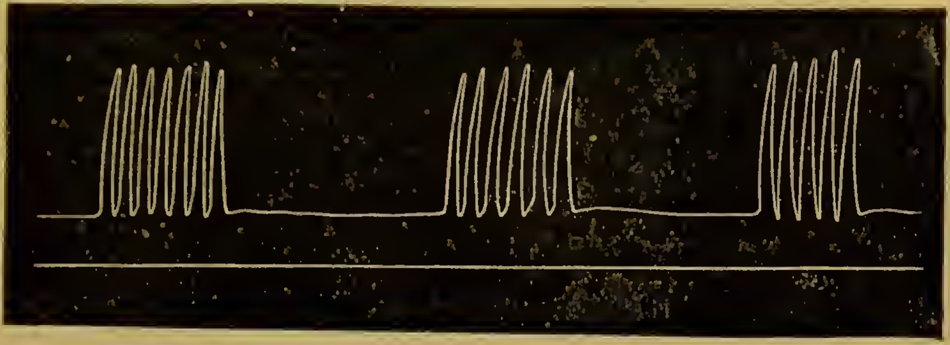


FIG. 104.—Periodic rhythm of the heart, the pulsations occurring in groups separated by intervals of complete quiescence.

the groups to appear, and a similar effect is produced if the blood is not renewed, but allowed to remain in the heart till it becomes venous.[2]

This periodic stage does not occur immediately after the heart has been tied on the cannula and supplied with serum. It is preceded by an initial stage, in which the beats are at first very quick, then slow, and these are separated by long pauses. Next comes the periodic stage in which the groups occur. It is succeeded by the stage of crisis in which the groups are replaced by single pulsations slower and smaller than the normal.

Atropine and nicotine do not prevent the occurrence of groups. Both of them make the groups longer and the pauses shorter. Atropine, however, even in small doses, soon kills the heart before it even enters on the stage of crisis. Nicotine, on the other hand, shortens the pauses, and rapidly induces the stage of crisis without destroying the energy of the heart, which is quite as great after poisoning by nicotine as in the normal condition.

Moderate doses of muscarine make the pulsations smaller and slower, the groups shorter, and the pauses longer. Sometimes the heart becomes exhausted before the stage of crisis appears, at other times it does not. Large doses of muscarine arrest the movements of the heart.

The activity of the heart which has been stopped by muscarine is again restored by atropine, but muscarine can render the beats smaller and slower, even after the previous application of atropine.

The occurrence of groups appears to be most probably due to interference of rhythms—of the ganglionic rhythm with that of muscular fibre.

We find an indication of alternate interference and coincidence of two rhythms in the alterations which sometimes occur in the beats of a ventricle containing its ganglia, but separated from the auricles. At first all the beats are of equal strength, but soon each alternate beat gets longer and shorter, till some disappear and others get much stronger than before (Fig. 105 ; cf. Fig. 64, p. 168).

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[1] Rossbach, *Ludwig's Arbeiten*, 1874, p. 92.
[2] *Ibid.*, p. 93.

Action of Drugs on the Vagus in the Frog.—When the vagi are stimulated by an induced current, the heart usually stops in diastole.

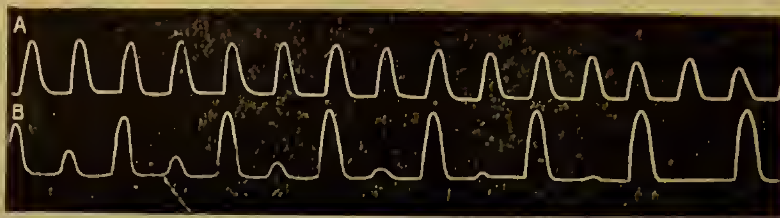

FIG. 105.—Tracing of the pulsations of a ventricle separated from the auricles by section at the auriculo-ventricular groove. After Ranvier, *Leçons*, 1877–78.

The effect of stimulation may be observed either on the heart simply exposed or by means of Ludwig and Coats' apparatus. The action of both vagi is not always alike. The right vagus has usually a greater power to arrest the heart than the left. The action of the vagus varies also according to the condition of the heart, and may produce different effects. It may cause, 1st, stoppage of the heart's beats, followed after an interval by slow pulsations or by small rapid pulsations, gradually becoming larger and stronger; 2nd, it may cause them to become small and slow without actual stoppage—this is the usual effect of irritation of the vagus in the living body; 3rd, it may cause the pulsations to become simply small and rapid without any stoppage; 4th, it may cause them to become rapid; 5th, it may cause them to become more powerful (Figs. 112 to 115, p. 324).

It may also act differently on the auricles and ventricle, producing still-stand of the ventricle and rapid pulsation of the auricles. These differences are probably due to a great extent to the vagus of the frog being really the combined vagus and sympathetic. At present the chief point upon which I wish to insist is that irritation of the **vagus** usually causes **still-stand** of the heart.

When the **venous sinus** is stimulated, still-stand of the heart is produced, which is even more complete and permanent than that which follows irritation of the vagus.

Action of Drugs on Inhibition of the Heart.—The effect of certain drugs upon the still-stand produced by irritation of the vagus or of the venous sinus is very remarkable. A large number of drugs, more especially atropine, curare, coniïne, and nicotine, when injected into the circulation have the power of completely destroying the inhibitory power of the vagi as far as the rate of rhythm is concerned, so that when their fibres are stimulated the heart is not arrested, nor are its beats rendered slower, but they are, on the contrary, quickened.

These poisons again may be divided into two classes:

Class I. containing atropine and its congeners.

Class II. containing curare, coniïne, nicotine, &c.

These two classes agree in destroying the inhibitory power of the **vagus** nerve, so that irritation of its trunk will no longer produce still-stand or slowing of the heart. They differ in their action on the still-stand produced by irritation of the **venous sinus.** Atropine and its allies prevent any inhibition occurring when the venous sinus is stimulated, or when muscarine is applied to the heart directly. This action affects chiefly the rhythm of the heart, for muscarine can still reduce the force of the cardiac contractions after the application of atropine.

Poisons of the second class do not prevent the still-stand of the heart occurring on irritation of the sinus, nor do they prevent muscarine from arresting the beats of the heart. This antagonism of atropine and muscarine has hitherto been explained on the supposition that muscarine greatly stimulates inhibitory centres in the sinus or auricle, while atropine paralyses them.

These two classes also agree in leaving unaffected the **accelerating** nerves of the heart.[1]

These complicated effects are very hard to explain on the ordinary hypothesis.

It is still more strange that although atropine and muscarine have such apparently opposite effects, they both agree in ultimately paralysing the inhibitory function of the vagus.

Muscarine, as I have already mentioned, arrests the movements of the heart; but, if the circulation be carried on, this arrest is only temporary, and is succeeded by a period, first of slowness, then of irregularity, and then of return to the normal; the stage of irritation of the inhibitory centre by the muscarine gradually passing into that of complete paralysis. During the time when the pulse is still slow in consequence of the action of muscarine, irritation of the vagus itself has no power to arrest it, or even to increase the slowness, while at that very time irritation of the accelerating nerves quickens its pulsations just as it would those of a normal heart.[2] When the accelerating nerves are thus irritated, there is often not only an increase in the number but also in the size of the pulsations, very much as Gaskell has observed under other conditions from irritation of the vagus in the frog. This action is only to be observed in moderate conditions of poisoning. When the poisoning is very profound, irritation of the accelerating nerves has a very peculiar

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[1] In the frog the accelerating nerves appear to run along with the inhibitory fibres in the vagus trunk. In warm-blooded animals these fibres run in separate nerves which pass out from the spinal cord along the vertebral artery and reach the heart through the sympathetic system. Although the chief accelerating fibres pass in these nerves, some are also contained in the vagus trunk, both in warm-blooded animals and in frogs. In animals poisoned by atropine, irritation of the vagus usually produces acceleration of the pulse.

[2] Weinzweig. From experiments in Von Basch's laboratory. *Archiv f. Anat. u. Phys.*, Phys. Abt., 1882, p. 527.

effect, sometimes producing so-called staircases, and sometimes a prolonged condition of still-stand, half in systole and half in diastole.

A marked **difference** is seen **between** the action of the **accelerating** nerves **and** the **inhibitory fibres** of the vagus, as the inhibitory action follows very shortly after the irritation of the vagus, and usually ceases very shortly after the irritation is removed, whereas that of the accelerating nerves does not occur until some time after the irritation has been applied, and often lasts a good while after the irritation has been removed. The two sets of fibres also appear to influence a different period of the heart's action, the inhibitory affecting the pause or relaxation, while the accelerating affect the systole or contraction. This condition renders it not improbable that we may have to do here with an action of these nerves on two different parts of the heart —the ganglia and the cardiac muscle.

It is quite clear that, in order to get any satisfactory explanation of these phenomena, we must take into consideration not only the rhythmical actions going on in the cardiac ganglia and those in the cardiac muscle separately, but also the relation to one another of these rhythms both as regards their energy and rate.

Theories regarding the Mode of Action of Drugs upon the Heart.

In order to explain the effects of various poisons upon the heart, a hypothetical view of its nervous system has been proposed by Professor Schmiedeberg,[1] and I have endeavoured to represent this in the accompanying diagram (Fig. 106).[2] It consists of a ganglion, M, which keeps up a rhythmical contraction of those muscular fibres of the heart to which it is connected by the fine nervous filaments, E. This ganglion is connected by an intermediate apparatus with an inhibitory ganglion, I, which can retard or stop the muscular contractions which M produces; and by another apparatus, C, with another ganglion, Q, which quickens the contractions. I is connected by an intermediate apparatus, A with the retarding fibres, V, of the vagus, and D with the quickening nerve, S, of the heart.

This schema has been adopted by Professor Harnack.[3]

It has been supposed that **motor ganglia** are present because the apex of the heart of the frog, which contains no ganglia, will

[1] Schmiedeberg, *Ludwig's Arbeiten*, 1870, p. 41.

[2] 'Experimental Investigations of the Action of Medicines,' Lauder Brunton, *British Medical Journal*, December 16, 1871.

[3] *Pharmakologische Thatsachen für die Physiologie des Froschherzens*, Halle, 1881.

not contract rhythmically if left entirely to itself, whereas the ventricle containing ganglia will do so.[1]

It has been supposed that **inhibitory ganglia** are present, because when a little muscarine is applied to the heart it causes

FIG. 106.—Diagram of the hypothetical nervous apparatus in the heart. M, motor ganglion. I, inhibitory ganglion. Q, quickening ganglion. V, inhibitory fibres; and S, quickening fibres from the head. A, A′, B, and C, intermediate apparatus. E, fibres passing from the motor ganglia, M, to the muscular substance, F. [For simplicity's sake only one set of motor ganglia has been represented, but other similar ones are supposed to be present in other parts of the heart, and so connected with this set that they all work in unison. It must be remembered that this diagram is purely hypothetical: but if this be carefully borne in mind, the sketch will be found of service in remembering and comparing the action of different poisons on the heart.]

it to stop in diastole. This effect is not developed all at once, but goes on gradually increasing, and its action in this respect seems rather to point to its effect upon ganglia than upon nerve fibres.

It has been supposed that the vagus acts through this inhibitory ganglion or ganglia because irritation of the vagus arrests the heart in diastole, just as muscarine does; but it has been supposed to be connected by some **intermediate apparatus** with the inhibitory ganglia, because we find that when nicotine is applied to the heart irritation of the vagus will no longer arrest its beats, but that irritation of the venous sinus, in which the inhibitory ganglia have been supposed to be situated, will do so at once.

It has been supposed that the inhibitory apparatus, I, was connected by an intermediate structure with the motor ganglia, M, because physostigmine does not produce the extraordinary still-stand which muscarine does, but it counteracts to a certain extent the effects of atropine which muscarine does not. Physostigmine in small doses increases the excitability of the vagus, so that a slight stimulus applied to that nerve, so slight that it would under ordinary circumstances be insufficient to affect the heart, will stop it.[2] In large doses it appears to paralyse the vagus. The difference of action between muscarine and physostigmine seemed to show that they acted on different nerve structures; while the mutual power of atropine and physostigmine

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[1] The recent researches of Gaskell have shown that the muscular fibre of the heart of the tortoise will contract, although it contains no ganglia. The question of muscular rhythm independent of ganglia will be considered further on.

[2] Arnstein and Sustschinsky, *Würzburger physiol. Untersuch.* iii.

to neutralise each other's effects within certain limits indicated that atropine acted on the same nerve structure as physostigmine and consequently on a different one from muscarine.[1]

When atropine is applied to the heart it completely removes the effect of muscarine and totally prevents any arrest being produced either by irritation of the vagus or the venous sinus. It has therefore been supposed that nicotine acts upon the intermediate apparatus, A, but that atropine acts either upon I or upon B.

The reason why it has been supposed that **quickening ganglia** exist is, that when irritation is applied to the vagus after its inhibitory power has been destroyed by the administration of nicotine or atropine it no longer produces slowness or still-stand of the heart, but, on the contrary, quickens its pulsations. But the **quickening** does **not** take place **immediately**, it only occurs some time after the application of the stimulus. If it is applied only for a short time, no quickening may take place until after its removal, but the quickening once induced remains for a considerable time. This seems to indicate that the stimulus does not act through nerve-fibres, as these would conduct the stimulus directly to the muscle, but rather through some ganglionic apparatus. It has been supposed that this apparatus is not identical with the motor ganglia themselves, because if the heart is irritated directly, its pulsations at once become quickened, and the quickening does not last long after the irritation is removed.

It is evident, however, that though this hypothetical schema allows us to explain in a fairly satisfactory manner the action of many drugs, yet it can only be looked upon in the same light as the hypothesis of cycles and epicycles in astronomy, which was useful for a time, and enabled astronomers not only to recollect but to predict facts. Its use was only temporary, and the hypothesis just at the time of its greatest complication gave place to one of the greatest simplicity.

It is probable, indeed almost certain, that the same thing will occur in regard to the action of drugs upon the heart, and that the whole complication of motor ganglia, inhibitory ganglia, accelerating ganglia, vagus endings, and intermediate fibres, may resolve themselves simply into a question of the mutual relationships between the rate of rhythm and rapidity of conduction in the muscular fibres, nervous ganglia, and nerve-fibres respectively. Schmiedeberg's hypothetical schema has been most useful for several years, but facts which it will not explain are beginning to accumulate, and we must look in another direction for their explanation. The whole question of the action of drugs upon the heart is far from being completely solved,

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[1] Lauder Brunton, *op. cit.*

but I shall try, if possible, to indicate the direction in which pharmacology is at present looking for an explanation.

For this purpose it will be necessary to go still more fully into the physiology of the heart than we have already done.

Before doing so, however, it may be advantageous to put in

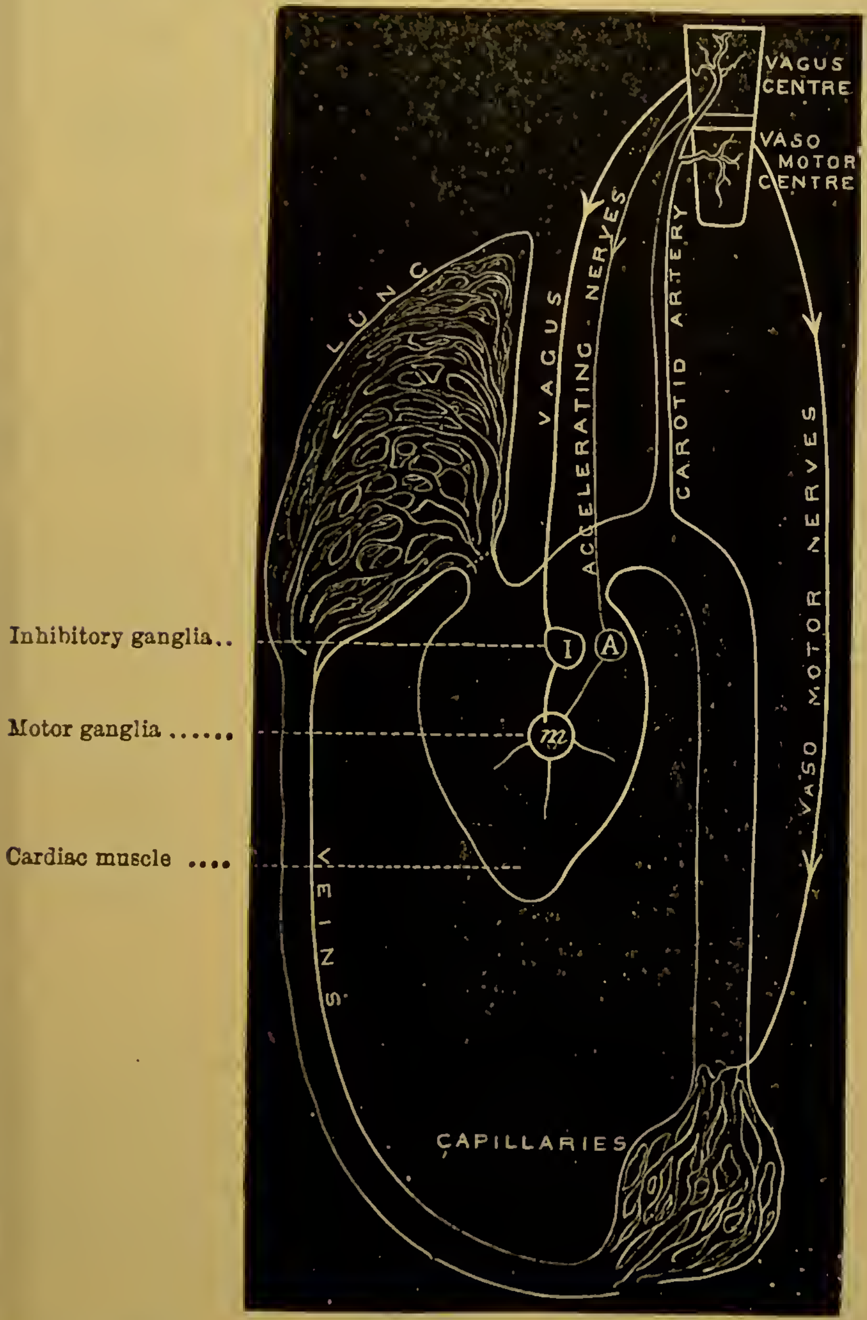

FIG. 107.—Diagram of the heart and vessels to illustrate the action of drugs on the various parts of the circulatory apparatus as given in the following tables. A, indicates accelerating ganglia.

a tabular form the action of the most important drugs on the various parts of the circulatory apparatus, according to the prevalent opinions at present.[1]

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[1] In drawing up this table [see pp. 316–319] I have been greatly aided by the admirable paper of Professor Boehm, read before the International Congress in London in 1881.

Cardiac Muscle.

STIMULATED BY.

[Stimulation is shown by increased energy of contraction, the rate of pulsation remaining the same or becoming slower.]

So-called cardiac poisons. With a larger dose the stage of stimulation is followed by one of peristaltic action, and final arrest in systole.[1]
- Digitalin.
- Digitaleïn.
- Digitoxin.
- Erythrophlœum.
- Helleboreïn.
- Nereïn (Oleander).
- Scillaïn.
- Antiarin.
- Strophanthus.
- Thevetine.
- Theveresine.

Veratrine.
Barium salts.
Caffeine (produces rigor).

In small doses:
- Potassium salts.
- Copper double salts.
- Zinc double salts.

These do not cause peristalsis, nor arrest in systole. They excite the heart to pulsate rhythmically, after it has been made to stand completely still in diastole by the application of muscarine.
- Guanidine.
- Physostigmine.
- Camphor.
- Monobromocamphor.
- Borneol.
- Arnica-camphor.
- Anilin sulphate.
- Cumarine.

DEPRESSED OR PARALYSED BY.

[Depression is shown by diminished energy of contraction with final stoppage in diastole. The cardiac muscle is shown to be paralysed by no longer contracting on stimulation, either mechanical or electrical.]

In large doses:
- Salicylic acid.
- Potassium salts.
- Copper double salts.
- Zinc double salts.

Quinine (?).
Saponin (removes the systolic still-stand produced by digitalin).
Apomorphine.
Emetine.
Muscarine.
Pilocarpine.
Veratrum viride (veratroidine and jervine).

Motor Ganglia.

[Stimulation is shown by increased rapidity and energy of contraction, which is observed, not only when the drug is given to an animal, but when it is applied directly to the heart.]

Alcohol group.
- Alcohol.
- Ether.
- Chloroform.
- Chloral.
- Anæsthetics generally.

Cyanogen.
Arsenic.
Quinine.
Guanidine.

[Depression is evidenced by slower and less powerful pulsations, with final stoppage in diastole. This stoppage is shown to be due to the action of the drug on the ganglia, and not on the cardiac muscle, by the heart contracting on stimulation, either mechanical or electrical, after spontaneous pulsation has ceased.]

Ergot.
Antimony (?). The stoppage in diastole caused by antimony is converted into stoppage in systole by helleboreïn.
Hydrocyanic acid.

The same drugs that stimulate in small doses depress when used in larger quantity, or at a later stage of their action.

[1] This stoppage of the heart in systole occurs in frogs, but in higher animals the heart may stop in diastole.

Inhibitory Ganglia.

STIMULATED BY.

[Stimulation is shown by the direct application of the drug to the heart, stopping its spontaneous pulsations completely, while it still contracts on the application of a stimulus either mechanical or electrical.]

Muscarine.
Pilocarpine.

DEPRESSED OR PARALYSED BY.

[Depression or paralysis is shown by stimulation, not only of the vagus trunk, but of the venous sinus itself, having lost all power to slow or stop the heart; and by the direct application of muscarine also having no action.]

Atropine.
Hyoscyamine.
Daturine.
Duboisine.
Cocaine.
Sparteine.
Saponin.

Vagus-ends in the Heart.

[Stimulation either of the ends of the vagus in the heart or of the inhibitory ganglia is shown by the injection of a drug rendering the pulse slow after previous division of the trunks of the vagi.]

Physostigmine (?).
It is said to render the peripheral ends of the vagus more sensitive, so that a slighter stimulus will stop the heart applied to the trunk.

[Depression or paralysis is shown by irritation of the vagus trunk no longer producing slowness or stoppage of the pulsations of the heart, while the application of muscarine, or irritation of the venous sinus, will still cause stoppage.]

Nicotine.
Saponin.
Lobeline.
Curare, methyl-strychnine, and probably large doses of all drugs which have the power of paralysing the ends of motor nerves.

Vagus Centre.

[Stimulation is evidenced by slowing of the pulse, disappearing on section of the vagi.]

Increased blood-pressure.
Venous blood.
Ammonia (in frogs).
Carbonic oxide.
Chloroform.
Chloral hydrate.
Butyl-chloral.
Belladonna (atropine).
Hyoscyamus (hyoscyamine).
Stramonium (daturine).
Aconite (aconitine).
Veratrum viride (veratroidine).
Tobacco (nicotine).
Digitalis (digitalin).
Hydrocyanic acid.

[Depression is evidenced by a quick pulse, which is not rendered slow by irritation of sensory nerves which usually produce slowing of the pulse, e.g. the central end of one vagus.]

Diminished blood-pressure and substances which produce it, e.g. nitrite of amyl and other nitrites.
Large doses of such substances as stimulate it in small doses, *vide* adjoining list.

Accelerating Centre.

STIMULATED BY.

[Stimulation is evidenced by the injection of the drug after previous section of the vagi rendering the pulse still more rapid than before.]

Irritants of motor centres.
- Venous blood.
- Ammonia.
- Cicutoxine.
- Caffeine.
- Delphinin.
- Picrotoxin.

DEPRESSED OR PARALYSED BY.

[Little or nothing is known about the depression of the accelerating centres.]

Saponin paralyses accelerating nerves.

Capillaries.

[Stimulation is shown by a rise in blood-pressure which remains after section of the spinal cord at the occiput, and is produced by the injection of the drug after previous division of the cord. It is also ascertained by the rate of flow through the vessels being diminished by the drug when circulation is kept up artificially in a frog whose nerve-centres have been destroyed, or in a single limb of a warm-blooded animal.]

Alkalies.
Digitalis and its allies.
Barium salts.
Potassium salts.
Copper.
Zinc, &c.

[Depression is shown by a fall of blood-pressure to a slight extent, even after the spinal cord has been divided, and by increased rapidity of flow when artificial circulation is kept up.]

Acids.
Nitrites.
Quinine (?)

Vaso-motor Nerves.

[It is very doubtful whether they are stimulated by drugs, and at any rate it is very difficult to ascertain whether any stimulation which may occur in the arterioles or capillaries is in the terminations of the vaso-motor nerves or in the muscular walls.]

[Paralysis is shown by the vessels not contracting on stimulation of the vaso-motor nerves, while they still contract on direct stimulation. This has been chiefly observed in the vessels of the intestines after irritation of the splanchnic nerves. The effect of irritation is ascertained by the alterations in colour of the intestines, and also by the alterations in the general blood-pressure which occur after irritation.]

Potassium salts.
Arsenic.
Antimony.
Mercury.
Iron.

Vaso-motor Centre.

STIMULATED BY.

[Stimulation is evidenced by a rise of blood-pressure, which disappears on section of the spinal cord below the medulla, and does not occur if the cord has been divided before the injection of the drug. This rule is only partially true, because subsidiary vaso-motor centres occur in the spinal cord itself.]

Irritants of motor centres, p. 176.

- Salts of ammonium.
- Potassium (?)
- Caffeine (?)
- Cicutoxine.
- Delphinin.
- Picrotoxin.
- Strychnine.
- Sanguinaria.
- Ergot (cornutine).
- Thebaine.

(Salts of ammonium … Thebaine:) Convulsants.

- Veratrine.
- Belladonna (atropine).
- Hyoscyamus (hyoscyamine).
- Stramonium (daturine).
- Carbolic acid (?)
- Salicylic acid.
- Turpentine.
- Camphor (rhythmically).
- Oil of rosemary, and other ethereal oils.

- Digitalin (?)
- Ether (?)
- Chloroform (?)
- Chloral (?)
- Butyl-chloral (?)

(Digitalin … Butyl-chloral:) Stimulant action doubtful; slight, and transient.

DEPRESSED OR PARALYSED BY.

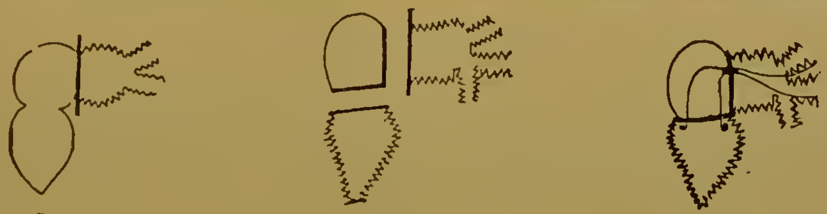
[Depression is evidenced by fall in the blood-pressure not depending on failure of the heart's action. It is also shown by the absence of rise in blood-pressure on irritation of a sensory nerve.]

Carbolic acid.
Lobelia.
Large doses of most drugs, such as those in the adjoining column, which stimulate in small doses.
Depression usually occurs in the later stages of the action of such drugs even in moderate doses.

Stannius's Experiments.

Some of the most important experiments relating to the action of the various cavities of the frog's heart were first performed by Stannius, and bear this name.

When the venous sinus is separated from the rest of the heart by cutting it off with a sharp razor, or by a ligature tightly drawn round it at its junction



a b c

FIG. 108.—*a*, diagram of frog's heart ligatured at the junction of the venous sinus with the auricles. The venæ cavæ and sinus are represented with a crenated outline resembling the tracing which their beats might give if recorded on a revolving cylinder. The auricle and ventricle being motionless would only trace a straight line if connected with a recording apparatus. Their outline is therefore represented by a straight line. *b*, diagram of a frog's heart in which sections have been made at the junction of the sinus with the auricles, and at the auriculo-ventricular groove. The sinus and ventricles pulsate, whilst the auricles remain motionless. The beats of the ventricle should have been represented as slower than those of the auricle, as in *f*, Fig. 109. *c*, the same as *b*, but with the parts of the heart separated by ligature instead of section.

with the auricle, it continues to pulsate, but the auricle and ventricle stand perfectly still (*a*, Fig. 108). If now the auricle is separated from the ventricle

by another cut (*b*, Fig. 108), or another ligature be applied (*c*, Fig. 108), at the auriculo-ventricular groove, the auricles remain motionless, but the ventricle begins to beat, so that the venous sinus and ventricle are both pulsating, while the auricles are at rest. The venous sinus and the ventricle, however, no longer beat with the same rhythm, and the rate of the ventricular beats is usually much slower (*f*, Fig. 109). In this remarkable experiment the complete stoppage of the auricles and ventricle which follows the removal of the venous sinus has been supposed to show that the motor centres for the entire heart reside in the sinus, and that from them the motor impulses originate which keep up the rhythmical pulsations of the organ. But the fact that the ventricles begin to pulsate on their own account when separated by another cut from the auricle seems to show that they also contain motor centres. The hypothesis has therefore been advanced that both venous sinus and ventricles contain motor centres, while the auricles contain inhibitory centres.

So long as the auricles are in connection both with the venous sinus and the ventricle, the motor centres in the latter two cavities are supposed to be sufficiently powerful to overcome the resistance offered by the inhibitory centres, and thus the cardiac rhythm is maintained. When the motor centres of the sinus are removed, the inhibitory centres of the auricle are supposed to be so powerful as to keep both it and the ventricle in a state of rest.

When the ventricle is separated from the auricles and their inhibitory influence removed, it again begins to pulsate rhythmically. In order to obtain a clearer idea of the mechanism of the heart, many variations of the above fundamental experiments have been made.

The chief results of these are the following :—

First, section or ligature of the venæ cavæ or of the venous sinus at any point before its junction with the ventricle does not affect the action of the heart (*d*, Fig. 109).

Second, section or ligature of the auricles at any point above the auriculo-ventricular groove arrests the movements of the part below them, while that connected with the venous sinus still continues to pulsate (*e*, Fig. 109).

d *e* *f*

FIG. 109.—*d*, diagram of heart with ligature round the venous sinus. *e*, diagram of heart with ligature round middle of auricles. *f*, diagram of heart with ligature in the auriculo-ventricular groove. The pulsations of the ventricle are much slower than those of the auricle and venous sinus. This is indicated by the larger dentation of the outline of the ventricle.

Third, irritation of the vagus nerves usually produces stoppage of the heart-beats.

Fourth, ligature or section of the vagi before their entrance into the heart prevents their having any action upon it when they are stimulated.

Fifth, ligature or section of the venous sinus or auricles prevents any action of the vagi upon the part of the heart below the ligature or section.

It is evident that section or ligature of the heart at any point between the junction of the sinus and auricles and the auriculo-ventricular groove has the same action on the movements of the part below it as irritation of the vagus.

But more than this; although, as we have seen, the motor ganglia of the heart appear to be situated chiefly in the venous sinus, yet **irritation of the sinus** produces **complete still-stand** of the heart, even more perfect and prolonged than irritation of the vagus. Strong stimulation of the venous sinus has therefore the same effect as its removal. The parts whose motions have been arrested by section or by irritation, in the experiment just de

scribed, are not paralysed: this is shown by the effect of stimulation upon them.

When the auricles and ventricle are standing still after section or ligature of the venous sinus, **irritation** of the outside of the ventricle with a needle has

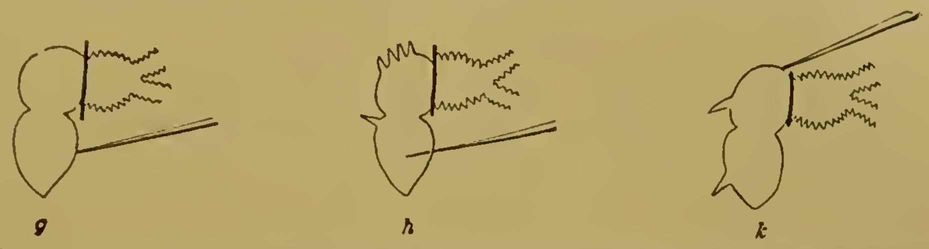


FIG. 110.—*g*, diagram of heart stopped by a ligature at the junction of the sinus and auricles. The *outside* of the ventricle is irritated by a needle, and the even outline indicates that no contraction occurs. *h*, diagram similar to *g*, but with the *inside* of the ventricle irritated by a needle. The projections on the outline of the heart indicate that one contraction of the ventricle and three or four of the auricles occur. *k*, diagram similar to *g* and *h*, but with the outside of the auricle stimulated by a needle. The projections indicate that one contraction of the auricle and one of the ventricle occur.

no action (*g*, Fig. 110); but if its interior be irritated by a needle (*h*, Fig. 110) the auricle contracts first, then the ventricle, then the auricle again two or three times, but the ventricle does not respond. When the auricle is irritated by a needle applied to its outside, contraction both of the auricle and ventricle ensues (*k*, Fig. 110). When the auriculo-ventricular groove is irritated by a needle there are usually eight or ten contractions in response. When the outside of the auricle is irritated by an interrupted current, numerous and rhythmical contractions both of auricle and ventricle ensue.

To sum up these results shortly, we find that either **removal of** the normal **stimuli** which pass in the direction of the circulation from the venous sinus to the auricle and then to the ventricle, or abnormally **strong stimulation**, produces arrest of the rhythmical movements of the heart, or, as it is usually termed, **inhibition.**

Some exceedingly instructive experiments have been made by Gaskell, who, instead of separating the cavities of the frog's heart from each other by sections or by a ligature, compresses more or less completely the point of junction, so as to impede or block (as it is termed) to a certain extent the transmission of stimuli from one cavity to another (Fig. 111).

FIG. 111.—Diagram to illustrate Gaskell's experiment. At *a* the jaws of the clamp hold the heart without compressing it, and each beat of the auricle is succeeded by one of the ventricle as shown by the figure $\frac{\mathrm{I}}{\mathrm{I}}$. At *b* the heart is compressed, and its rhythm disturbed, so that one beat of the ventricle only occurs for several of the auricles.

He does this by a clamp the two limbs of which are placed one on each side of the heart. By means of a micrometer screw their edges can be approximated so as either simply to hold the heart without pressure or to compress it to any desired extent. When the clamp is placed in the auriculo-ventricular groove, the beats of the auricles and ventricle are registered separately by levers above and below the clamp with which the auricles and ventricle are connected by threads.

When the heart is simply held by the clamp without compression, each beat of the auricle is followed by one of the ventricle; but when the auriculo-ventricular groove is compressed the transmission of stimuli from the auricle

to the ventricle appears to be blocked in somewhat the same way as it is by compression in the contractile tissue of medusæ, and one beat of the ventricle then occurs with every second, third, fourth, or more auricular beats, according to the degree of pressure, and if this be very great the ventricle will cease beating altogether.

The beats of the ventricle are shown in this experiment to be diminished or arrested by hindering or blocking the transmission of stimuli to it from the venous sinus and auricle. But, as one might expect, a diminution of the stimuli themselves has a similar effect as a block to their passage. Thus, if the auricle and sinus are heated, but not the ventricle, their rhythm is markedly quickened, but the ventricle now beats only once for every two or even more pulsations of the auricle, the heat appearing to render the impulses proceeding from the auricle and sinus more rapid but more weak. If the ventricle be heated as well, it will respond to each beat of the auricle, so that the whole heart beats more quickly, but if the ventricle alone be heated its rhythm remains unchanged.

Experiments which are likely to give useful information in regard to the action of various drugs on the cardiac muscle and nerves have been made by Gaskell by the aid of the clamp already described.

General Considerations regarding the Heart.

In ascidians the heart is a mere contractile sac open at both ends, and drives the fluid alternately in opposite directions. In snails it is a simple sac of protoplasm without differentiated nerves, but it drives the nutritive fluid in one direction. In the amphioxus there is no special heart, but only numerous contractile dilatations in the chief blood-vessels. In fishes the heart may be said to consist of three parts—the auricle, ventricle, and arterial bulb. The heart of the frog has already been described, and that of mammals requires no description.

Even the complicated mammalian heart may be regarded as a special development of the simple contractile tube endowed with the power of peristaltic contraction. The direction in which the contraction occurs is probably determined at first by slight differences in the stimuli to which the two ends of the tube are subjected, and the direction may be altered by altering the stimulus. Thus in the heart of a fish the contraction usually proceeds from the auricle to the ventricle and bulb, but by irritating the bulb the direction may be reversed so that the bulb contracts first and the auricle last, and this reversal of rhythm may persist for some time.[1] In the mammalian heart it is not perhaps so easy to reverse the rhythm by simple irritation, and probably some interference with the cardiac nervous system is also requisite, but by introducing tincture of opium into the mammalian ventricle the rhythm may be reversed so that the beats of the auricle follow instead of preceding those of the ventricle.[2]

The **cause of rhythmical pulsation** in the heart is usually supposed to be the motor ganglia which it contains. Of late years numerous researches have shown that, although these are very important indeed, yet they are not to be looked upon as the exclusive originators of the rhythm. The heart of the snail, although it consists of simple protoplasm without nerves, beats rhythmically, and when a ligature is tied across the venous sinus in the frog the venæ cavæ and upper part of the sinus continue to beat although they possess no special ganglia. while the rest of the heart remains motionless although it contains both Bidder's and Remak's ganglia. From this experiment one would be inclined at first to say that the **initiation of rhythm** in the heart is due to the **muscular tissue** of the venæ cavæ and sinus,

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[1] Gaskell, *Journ. of Physiol.*, vol. iv. p. 78.
[2] Ludwig, *Physiologie*, 1861, vol. ii. p. 88.

and might be inclined to regard the **nervous system** of the heart as an apparatus for **merely conducting** stimuli from the sinus to the auricles and ventricle.

Other experiments would seem to deprive the nerves even of this function, for Engelmann [1] and Gaskell have shown that when Bidder's ganglia are excised, or the nerves cut through as they traverse the auricles, contractions still pass from the venous sinus to the ventricle, and continue to do so when the nerves have not only been divided but most of the muscular tissue of the auricle has been cut through and only a narrow bridge remains behind. This may seem to prove that the muscular tissue of the heart conducts the motor stimuli from the venous sinus to the auricle and ventricle, which cause them to contract, and may appear to show that the cardiac nerves are entirely superfluous. A similar mode of reasoning, however, would lead us to say that the ganglia in medusæ are also superfluous because the contractile tissue will pulsate rhythmically after they have been cut off, if it be placed in acidulated water.

In regard to the **conduction of stimuli**, the fact probably is that under favourable conditions they may be conveyed by the muscular tissue alone from the sinus to the ventricle, but under ordinary circumstances they are conveyed in part, at least, by the nerves.

Ganglionic tissue is more sensitive than contractile tissue, and the stimuli which act on the ganglia of the medusa, under the conditions in which it lives, are insufficient to excite contractile tissue. When the ganglia are paralysed by a poison, the effect is the same as if they were cut off, and pulsation is arrested. A similar condition appears to occur in the ventricle. The muscular tissue forming the apex of the frog's heart under ordinary circumstances will not beat when separated from the rest unless an extra stimulus be applied to it. The ventricle containing Bidder's ganglia will usually pulsate rhythmically, and if its apex be dipped in a solution of chloral no effect is produced, but if its base be dipped in the solution so that the drug acts upon the ganglia, the pulsations are arrested apparently by paralysis of the ganglia (Harnack).

We may consider, then, that ganglia are more susceptible to stimuli than muscular fibre, and have the function of making it pulsate rhythmically when it otherwise would not.

It is probable also that they serve to prevent the occurrence of blocks at the junction between the different cavities of the heart which might occur if the stimuli were transmitted from each cavity by muscular tissue alone.

When the **heart is dying**, and when we may fairly assume that its nerves are losing their functional activity, such blocks actually take place, and the ventricle may beat only once for every two or three or more beats of the auricle.

The cardiac muscle is also without doubt losing its functional activity, yet it still retains it to such an extent that each cavity can contract powerfully. The same thing occurs when the heart is poisoned with chloral, iodal, or other members of the same group, which, as already mentioned, paralyse the cardiac ganglia.[2]

In the present state of our knowledge it is difficult to make any absolute statement regarding the function of the **cardiac ganglia**, but I think we may fairly assume them to have two **functions**, (1) to originate rhythmical pulsations in the heart when the muscular fibre alone, although capable of independent rhythmical pulsation, would not pulsate under the conditions which may be present; (2) to transmit and receive stimuli from one cavity of the heart to the other, and thus prevent the occurrence of blocks at the junction of the cavities and consequent irregular action which might occur if the stimuli were transmitted only by the muscular fibre.

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[1] Pflüger's *Archiv*, xi. p. 465.
[2] Harnack and Witkowski, *Arch. f. exp. Path. und Pharm.*, vol. xi. p. 15.

Regulating Action of the Nervous System.

The necessity of some means for regulating the action of the heart in accordance with the wants of the body is obvious, and in the heart we find that such an arrangement exists in relation both to the strength and rate of pulsation.

The **action of the vagus** upon the heart has long been a matter of great dispute, some physiologists holding it to be the motor nerve of the heart, while the majority regard it as inhibitory. The reason of this disagreement probably is that the right and left vagi have frequently different effects upon the heart, and that the effects even of the same vagus may vary according to the state of nutrition of the heart, and other circumstances. We find for example in rabbits that both the right and left vagi can usually slow or stop the heart; but sometimes the right has much greater power in this respect than the left, and in some species of tortoise the left vagus has no inhibitory action upon the heart at all, and in the frog during the breeding season the action of the vagi is very uncertain. The cause of these different results appears to be that the vagus is a very complex nerve, and contains accelerating and strengthening fibres which are derived from the sympathetic, as well as inhibitory fibres which are derived from the spinal accessory, and sensory fibres which belong to the vagus proper. The results of stimulating the vagus trunk will vary according to the proportion of these different fibres which it contains, and on the activity of each kind at the time of stimulation.

A number of experiments made by Gaskell on the heart *in situ* and with the clamping apparatus already mentioned, by which the beats of the auricle and ventricle may be simultaneously recorded, have led him to divide the effects produced on the heart by irritation of the vagi into two types: (*a*) affections of the **rate** of rhythm; and (*b*) affections of the **strength** of the contractions.

The effect of vagus stimulation on the heart of the frog may be divided into five classes.

The 1st class is that which occurs with the heart of the tortoise or frog *in situ* or just after removal from the body. The vagus here causes arrest by **slowing** the rate of **rhythm**; and, in consequence, the first beats which occur after the heart again begins to beat are slower than those preceding the stimulation.

In the next classes the vagus produces its effect by **weakening** the **strength** of the contractions so that they may become invisible and the heart remains still, but after it begins to beat their rate is as quick or quicker than before.

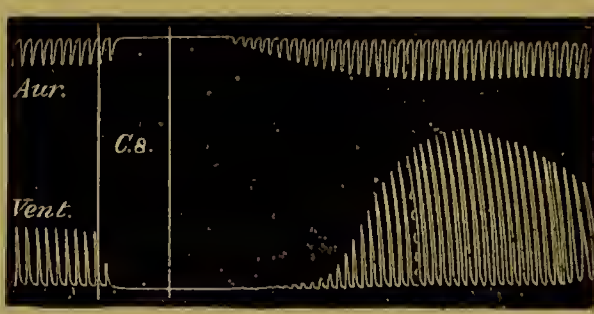

FIG. 112.—After Gaskell. Tracing showing the action of the vagus on the heart. *Aur.* indicates the auricular, and *Vent.* the ventricular tracing. The part included between the upright lines indicates the time during which the vagus was stimulated. *C.* 8 indicates that the secondary coil used for stimulation was eight centimètres distant from the primary. The part of the tracing to the left hand shows the regular contractions of moderate height before stimulation. During stimulation, and for some time after, the movements of both auricle and ventricle are entirely arrested. After they again commence they are small at first, but soon acquire a much greater amplitude than before the application of the stimulus.

The 2nd class is an example of this. In it irritation of the nerve produces complete stoppage of both auricles and ventricles. This is followed by con-

tractions, which are at first so small as to be hardly visible, but quickly grow larger until they are much greater than the normal; from this they gradually decrease to the normal size (Fig. 112).

The two types of action may occur together, the rhythm becoming slower and the contractions smaller. This is seen in Fig. 113.

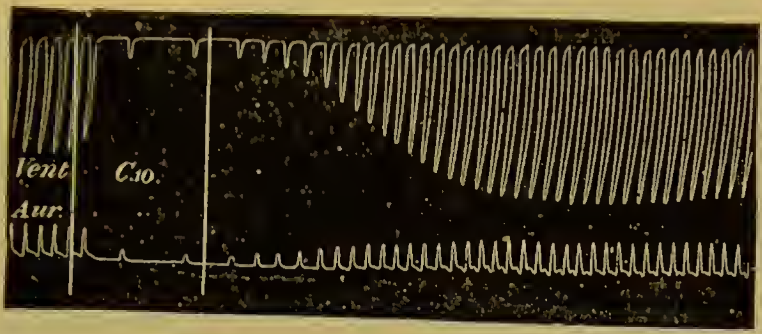

FIG. 113.—After Gaskell. Tracing showing diminished amplitude and slowing of the pulsations without complete stoppage, during irritation of the vagus.

The 3rd class is where irritation produces no still-stand of either auricles or ventricles, but only great diminution in the size of the beats, followed by a gradual increase and subsequent fall similar to that just described. This curve is like the first, but differs from it in the absence of the complete arrest (Fig. 114).

FIG. 114.—After Gaskell. Tracing showing diminished amplitude of contraction without slowing or stoppage during irritation of vagus.

The 4th is that where there is no primary diminution, but gradual increase in the size of the beats, which again sink to the normal (Fig. 115).

The 5th is where irritation of the vagus does not stop the beats of the venous sinus but causes both auricles and ventricle to stop.

The ordinary inhibitory effect of the vagus is the one which is noticed best in well-nourished hearts, and as the heart becomes more exhausted, and is dying, the motor power of the vagus becomes more and more pronounced. We find a similar occurrence in the case of the splanchnics, which lose their inhibitory power as the intestine dies. Nervous structures as a rule die sooner than muscle, and the conclusion is not unwarranted that the disappearance of the inhibitory action of the vagus is due to a gradual death of the nervous structures upon which it acts in the healthy heart, while its action on the muscular tissue, which has a more prolonged vitality, still remains. The actual increase, indeed, in its motor action we may attribute to the removal of nervous interference.

Hypothesis regarding the Action of the Vagus.—Nervous interference as a cause of inhibition was clearly pointed out by Bernard, and in the case of the heart has been discussed by Ranvier with his usual clearness. In the grey matter of the spinal cord there is ample room for the slowing

of nervous stimuli by transmission along paths of different lengths (p. 169), more especially as a small length of grey matter is equivalent to a great length of ordinary nerve-fibre (p. 162).

In the heart we might suppose there was no such provision, but, as Ranvier points out, the ganglion cells in the auricle have one of their fibres wound

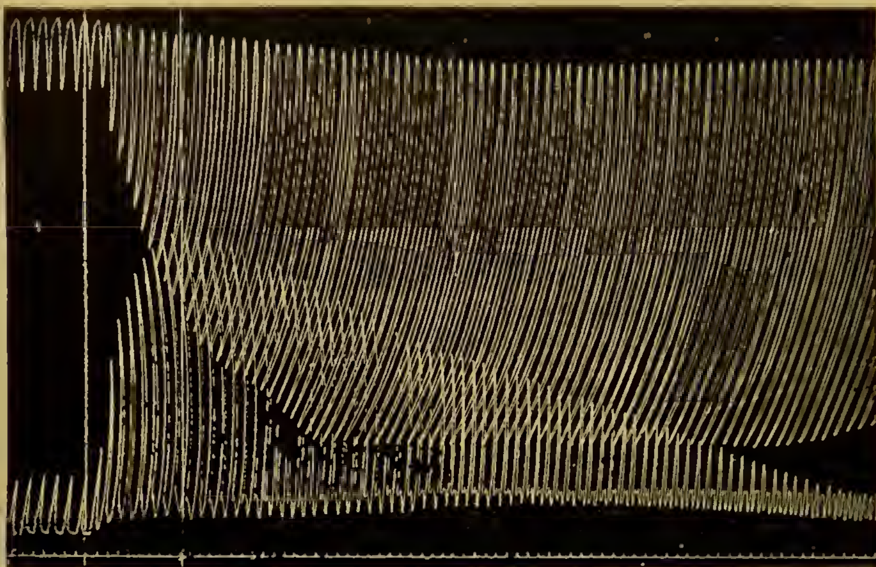

FIG. 115.—After Gaskell. Tracing showing increased cardiac contractions from irritation of the vagus. [In this figure the upper tracing shows the ventricular and the lower the auricular contractions.]

spirally, so as to give a great length in small space, and thus provide for retardation and interference of stimuli (Figs. 116, 117). If we suppose that some of the nerve-fibres contained in the vagus trunk pass through these spiral ganglia while others pass on directly to the heart, we can understand that the different rates of transmission may lead to interference and stoppage of pulsation. Alterations in the rate of transmission along the spiral fibre may again convert interference into coincidence of waves and cause acceleration and increased action. If these spiral fibres are affected by drugs so that the rate of transmission of stimuli along them is altered, we can understand that the interference may in some cases be increased, in others diminished, and that an increase of interference may readily pass into the opposite condition, so that the irritation of the vagus no longer produces stoppage but acceleration of the heart, such as actually occurs on irritation of the vagus after its inhibitory power has been paralysed by atropine.

We can understand also how curare and the large class of drugs which paralyse the motor nerves may destroy the inhibitory power of the vagus.

Inhibition in the Heart.—But it is probable that interference between the nervous structures is not the sole cause of inhibition in the heart; we must look also to the relationship between nervous and muscular rhythms. Thus distension of the ventricle frequently diminishes or abolishes the action of the vagus, the stimulus which the pressure within the heart exerts on the muscular fibre appearing to more than counteract the inhibitory action of the nerve. The condition of the muscular fibre too is probably very important. Thus, feeding the frog's heart with a solution containing soda appears to paralyse the power of the vagus, which is again restored by potash.[1] (Compare their action on the cardiac muscle, p. 307.)

It is indeed to an action on the muscle rather than on the nerve that we must probably look for the explanation of the action of atropine. For the heart in snails, though apparently destitute of both ganglia and nerves, is arrested by an interrupted current. This effect is prevented by atropine.

[1] Lowit, *Pflüger's Archiv*, xxv. p. 466.

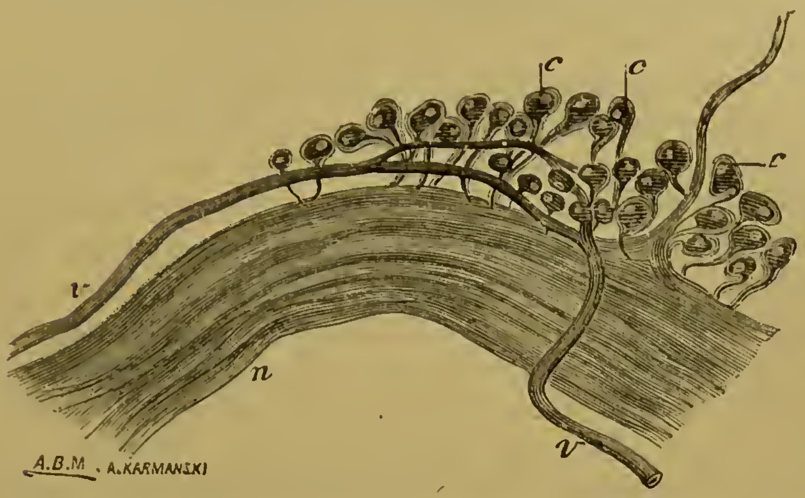

FIG. 116.—Part of the posterior cardiac nerve, highly magnified, showing the ganglia.[1]

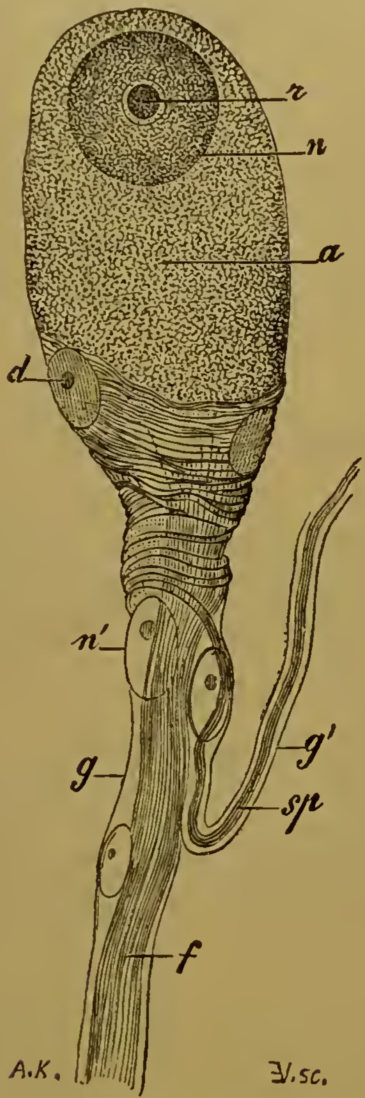

FIG. 117.—Spiral ganglion cell from the pneumogastric of the frog. This figure is not taken from the cells in the cardiac nerves, as in them the connection between the spiral and straight fibres has not been clearly made out, but it is probable that these cells have a structure similar to the one figured (Ranvier, *op. cit.* pp. 114-120). *a* is the cell-body, *n* the nucleus, *r* the nucleolus, *d* nucleus of the capsule, *f* the straight fibre, *g* Henle's sheath, *sp* spiral fibre, *g'* its *gaine*, *n'* nucleus of Henle's sheath.[2]

[1] Ranvier, *Leçons d'Anatomie Générale*, année 1877–78, p. 106.
[2] *Ibid.*, p. 114.

It is exceedingly difficult, or perhaps impossible, with the physiological data which we at present possess, to give a complete and satisfactory explanation of the action of drugs on the heart, but it is evident that while all new discoveries tended for a while to render our ideas regarding the cardiac mechanism more and more complicated, our increasing knowledge now tends to render them more simple. Before long we may hope that systematic investigations into the action of drugs on the excitability, rhythm, and power to conduct stimuli of the cardiac muscle itself, on the action of drugs upcn the rhythm of the ganglia, and on the rate of transmission by the nerves, as well as on the mutual relations of these various factors, will at last give us a clear understanding of this very difficult and complicated subject.

Therapeutic Uses of Drugs acting on the Circulation.

The drugs which act on the circulation have been divided according to their action into stimulants, tonics, and sedatives. Each of these classes has been further subdivided into cardiac and vascular, according as its members act on the heart and vessels. There are thus six subdivisions in all: cardiac stimulants, vascular stimulants, cardiac tonics, vascular tonics, cardiac sedatives, and vascular sedatives.

Cardiac Stimulants.

These are substances which rapidly increase the force and frequency of the pulse in conditions of depression. The most important are ammonia, and alcohol in its various forms, but there are also other substances which are sometimes useful.

Heat.

Liquor ammoniæ. B.P. Aqua ammoniæ. U.S.P.
Ammonium carbonate.
Sal volatile (spiritus ammoniæ aromaticus).
Alcohol.
Brandy.
Whisky.
Eau de Cologne.
Gin.
Liqueurs.
Strong wines
Atropine.
Ether.
Chloroform.
Spirit of chloroform.
Spirit of ether.
Camphor.
Aromatic volatile oils.
Oil of turpentine.
Heat and counter-irritants to the præcordium.

Cardiac stimulants are used to prevent or counteract sudden failure of the heart's action in syncope or shock due to mental

emotion, physical injury, or poisoning by cardiac depressants, or by the bite of snakes, or when the action of the heart becomes much depressed in the course of fevers or other diseases.

Although alcohol after its absorption stimulates the heart, yet its effect on the heart is probably, to a considerable extent, due to a reflex action on it through the nerves of the mouth, gullet, and stomach. Its action is consequently very rapid, and begins before there has been time for much of it to be absorbed. On this account, however, it must be given in a somewhat concentrated form, and if much diluted, as in the form of weak wine or beer, which has little or no local action and can exert no reflex action, it has little or no power as an immediate stimulant. When given in disease it is best to administer it in small quantities frequently, and the rule by which to ascertain whether it is doing good or not is: Does it bring the circulation more nearly to the normal or not? If it does so, it is beneficial; if it does not, it is harmful. Thus, if the pulse be too quick, alcohol should render it slower; if already abnormally slow, alcohol should make it quicker. If too small, soft, and compressible, alcohol should render it larger, fuller, and more resistant. There are other rules connected with the effect of alcohol on other organs which also regulate its use in disease, but these will be given further on.

Ether alone or mixed with alcohol has a stimulant action almost more rapid than alcohol itself; and chloroform in small doses, and especially when mixed with alcohol, is also a powerful stimulant.

Ammonia has not only a reflex action on the heart like that of alcohol, but has powerful stimulating action on the vaso-motor centre. Its action when applied to the nose in syncope has already been discussed. In cases of snake-bite thirty minims of liquor ammoniæ have been injected directly into the veins. The immediate stimulating effect appears to be beneficial, although it is doubtful whether life can really be saved by this means.

Camphor is useful as a cardiac stimulant in febrile conditions with a tendency to failure of the circulation, as in typhus and typhoid fevers; in exanthemata, when the rash does not appear; in asthenic pneumonia, and in the typhoid condition depending on other diseases.

Aromatic volatile oils and substances containing them have also been used in similar but less severe conditions.

One of the most powerful of all cardiac stimulants is heat, and when the heart's action threatens to fail it may be frequently restored by warm fluid taken into the stomach, or by the application of an indiarubber bag[1] or bottle filled with hot water, or

[1] An indiarubber bag for holding hot water is one of the most useful things an invalid can carry about with him. It should have a flannel case fastened by buttons

of a bag filled with hot sand or salt, or of a hot poultice to the cardiac region.

It must be remembered that the high temperature of the body in febrile conditions acts as a cardiac stimulant; and if this stimulus be removed by the temperature falling, either in the natural course of the disease or in consequence of the administration of antipyretics, the heart may fail and collapse, and death ensue, unless it be stimulated either by medicines or by the application of heat to the cardiac region.

Vascular Stimulants.

These are substances which cause dilatation of the peripheral vessels,[1] and thus render the flow of blood through them more rapid. The most important are:

Heat.

Alcohol in its various forms.	Dover's powder.
Ether.	Acetate of ammonium.
Nitrous ether.	

Alcohol and ether, by stimulating the heart at the same time that they dilate the vessels, render the peripheral circulation very vigorous. From its stimulant action on the vaso-motor centre, ammonia is less useful than alcohol.

Vascular stimulants are useful in equalising the circulation and preventing congestion of internal organs. Thus, from exposure to cold generally so that the whole surface of the body is chilled, or from a local chill due to a draught, or to the combined action of cold and moisture, as in wet feet, congestion of the respiratory tract, or of the stomach, intestines, or pelvic organs may occur. This frequently evidences itself immediately either by rigors or by localised pain. If the congestion be not relieved inflammation may occur, but if alcohol be taken either in a concentrated form or diluted with boiling water, the vessels of the surface dilate, a warm glow is felt throughout the body, the shivering and pains disappear, and frequently all injurious results of the chill are averted. If the external cold, however, is very excessive, and the exposure is to be prolonged, alcohol must be

so that it can easily be removed. This allows the heat to come gradually through without burning the skin. For a small gratuity the engine-driver or stoker is usually willing to fill the bag with hot water, and the bag can be refilled if necessary at each station where there is a sufficiently long stoppage. This is sometimes a very great boon to invalids on long railway journeys such as they are often compelled to make on their way to winter health resorts.

[1] From this definition it will be observed that while cardiac stimulants increase the functional activity of the heart, vascular stimulants do not increase the contractile power of the vessels, nor the activity of the vaso-motor centre, but, on the contrary, diminish the contraction of the vessels.

used with great care, as the blood becomes much more rapidly cooled when the cutaneous vessels are dilated than when they are contracted; and in arctic temperatures a person is much more readily frozen to death after the free use of alcohol. Dover's powder is also a useful vascular stimulant, though less powerful and rapid than alcohol. It is of use in similar cases to those just described, and may be given after the alcohol to supplement and continue its action.

Slighter cases of chill may be treated by Dover's powder alone, and ten grains of it taken at night will often cut short commencing coryza, and will frequently prevent slight increase of consolidation occurring round a cavity after a chill in persons suffering from phthisis. Patients suffering from this disease should not omit to take a Dover's powder or some other vascular stimulant at night whenever they feel as if they had caught cold, and before any local mischief can be detected.

All nitrites dilate the blood-vessels and thus act as vascular stimulants. The one most commonly employed is nitrite of ethyl in the form of spirits of nitrous ether. This remedy, taken in hot water or along with acetate of ammonium, is a useful vascular stimulant, and is often used for the same purposes as Dover's powder.

Camphor is frequently used as a popular remedy instead of alcohol or Dover's powder in order to cut short coryza or catarrh, about ten drops of the tincture being taken on a piece of sugar. Local vascular stimulation is useful in removing chronic inflammation or consolidation. For a more detailed account of its action and uses, *vide* Irritants and Counter-irritants (p. 343).

Cardiac Tonics.

These are drugs which have no perceptible immediate action on the heart, but when given for a little while render its beats much more powerful, although usually much slower. The most important of them are :—

- Digitalis.
  - Digitalin.
  - Digitalein.
  - Digitoxin.
- Erythrophlœum (Casca)
  - Erythrophlœin.
- Strophanthus hispidus.
  - Strophanthin.
- Convallaria majalis.
  - Convallamarin.
- Adonis vernalis.
  - Adonidin.
- Squills.
  - Scillaïn.
- Helleboreïn.
- Antiarin.
- Caffeine.
- Nux vomica.
  - Strychnine.

All these drugs, as already mentioned, stimulate the cardiac muscle and render its contractions slower and stronger. Although in large doses they tend themselves to produce irregular and peristaltic contraction of the heart, yet in moderate doses they tend to remove irregularity already present. The cases in which they are most useful are those in which the left ventricle is unable to drive the blood with sufficient force into the aorta. It is evident that this inability may depend on simple weakness of the ventricle without any valvular lesion, or upon irregular action of the various cavities, or upon valvular lesions, or on a combination of two or more of these conditions.

Weakness of the heart may occur in cases of general malnutrition, as anæmia and chlorosis, or in consequence of acute disease such as fevers. It is not necessarily accompanied by dilatation, but if it continues for some time the cavities are apt to dilate. A considerable amount of dilatation may sometimes occur without leading to valvular incompetence, but if it proceeds beyond a certain point the cusps of the tricuspid and mitral valves become insufficient to close the dilated orifices, and mitral or tricuspid regurgitation is the result. For it must be remembered that in the healthy heart the tricuspid and mitral orifices are much diminished in size by the contraction of the muscular tissue of the heart at the moment of systole.

In cases where the mitral valve is thus affected, a systolic murmur may be heard at the apex during life, but, should death occur, the valves may be found perfectly competent to close the mitral orifice in the heart, which is then in a state of more or less complete rigor. In all such cases of weakness of the heart, either with or without dilatation and functional incompetence of the valves, digitalis is of the greatest possible service. I have also found erythrophlœum give most satisfactory results in simple dilatation without incompetence.

The form of valvular disease in which cardiac tonics are especially useful is mitral regurgitation. In all forms of valvular disease there is a tendency to the occurrence of compensatory hypertrophy, which will enable the heart to do its work in spite of the hindrance caused by the disease. Wherever this is sufficient, so that the circulation is well carried on, notwithstanding the valvular defect, cardiac tonics are useless and likely to be injurious. Nor should they be given when the compensatory hypertrophy is just beginning to take place. But when compensation is insufficient, cardiac tonics are of the very highest value. In mitral regurgitation the blood, instead of being driven entirely onwards by the left ventricle into the aorta, is partially driven backwards into the left auricle at the very moment that the right ventricle is driving the blood into the pulmonary artery and lungs. Hence there is a tendency to pulmonary congestion, which may lead to hæmoptysis. The right ventricle having to work

against greatly increased pressure tends to dilate, the blood accumulates in the venous system generally, and venous congestion of the stomach leads to loss of appetite, of the kidneys to albuminuria, and of the limbs to anasarca. While the venous system is gorged, the arterial is correspondingly empty, and it is not only the stomach, kidneys, and limbs which suffer by the stagnation of the circulation, for a similar condition exists in the heart itself. In consequence of this its action may become not only weak but irregular, and matters go on from bad to worse.

In such a condition cardiac tonics are of the greatest possible service. By increasing the strength of the cardiac muscle they not only enable the left ventricle to drive a larger proportion of blood into the aorta, but they actually tend to lessen the opening of the mitral orifice in the same way as in functional incompetence. By rendering the pulse less frequent they allow the ventricle to become more completely filled during each diastole. The pressure on the lungs, right side of the heart, and venous system is diminished, the arterial system becomes correspondingly filled, the congestion of the various organs is diminished and their function correspondingly improved.

The consequence of this is, that in the stomach we have increased appetite, in the kidneys diminished albumen, and in the limbs removal of anasarca. The heart also benefits by the improved circulation in it, its pulsations are more regular and powerful, and it will often continue to act well and carry on the circulation satisfactorily even after the tonics which first enabled it to do so have been discontinued.

In mitral stenosis cardiac tonics probably are beneficial both by lengthening the diastole, and thus allowing more time for the blood to run out of the auricle into the ventricle, and by strengthening the auricle itself. Besides this, mitral stenosis is usually accompanied by mitral regurgitation, which will be benefited by cardiac tonics in the way just described.

In aortic stenosis digitalis is of little or no use when there is sufficient compensatory hypertrophy, but may be useful if the heart is becoming feeble.

There has been considerable difference of opinion regarding the use of digitalis in aortic regurgitation, some holding it to be useful and unattended with any risk, while others regard its administration as attended with considerable danger. In considering this question we must bear in mind that the risks which a patient runs from aortic regurgitation are not the same in all stages of the disease. While the aortic regurgitation is uncomplicated, and the ventricle strong enough to carry on the circulation, the risk to the patient is that of sudden death by syncope.

It is easy to understand how this should be the case. When

the aortic valves are healthy the arterial system may be regarded as a large-branched tube open only at one end—the capillaries—and through these the blood flows so slowly that there is no risk of syncope from the blood-pressure falling too low (Fig. 118, *a*).

In a case of aortic regurgitation, on the contrary, the arterial system is open at both ends, and during the cardiac diastole the blood is not only running through the capillaries, but is running backwards into the left ventricle, so that the conditions are favourable for the blood-pressure falling so low as to induce syncope (Fig. 118, *b*). It is evident that anything which prolongs the diastole, and thus allows more time for the arterial system to empty itself through the capillaries at one end and into the ventricle at the other, will increase the risk of syncope, and for this reason digitalis cannot be regarded as free from danger in aortic regurgitation. The danger may, however, be very considerably diminished

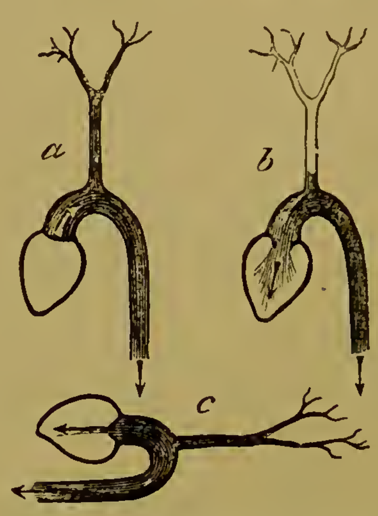

FIG. 118.—Diagram to illustrate the tendency to syncope in aortic regurgitation. In *a* the aortic valves are healthy and prevent regurgitation. The carotid and its branches are shown as full. In *b* there is aortic regurgitation, the blood flows out of the arterial system through the capillaries and into the heart. The carotid and its branches are shown as empty. In *c* the condition is the same as in *b*, but the patient is supposed to be in the recumbent posture, and the carotid and its branches remain full.

by keeping the patient in a recumbent posture with the head low. The column of blood above the aortic valves being lower, there will be somewhat less tendency to regurgitation; and even should the arterial pressure fall much, the brain may still receive sufficient blood supply to prevent syncope.

In cases of aortic disease, where compensatory hypertrophy is insufficient, or where the hypertrophied heart is becoming enfeebled and dilated so that the mitral valves no longer close the orifice, the most urgent risk to the patient is no longer that of sudden syncope, but of pulmonary embarrassment, dropsy, and all the other consequences of mitral regurgitation. In such cases, as well as in those where organic disease of both mitral and aortic valves exist simultaneously, we must treat the urgent symptoms and give digitalis or other cardiac tonics.

In dilatation of the right heart due to bronchitis or emphysema, digitalis is frequently useful, though its benefit is less marked than in mitral disease.

Risks attending the Administration of Digitalis and other Cardiac Tonics.—The great risk attending the use of these drugs is sudden death from syncope. Whenever it is necessary to push them to any extent, the patient should be kept strictly in the recumbent posture, and not allowed to raise himself quickly even into a sitting position on any pretence whatever, even when there is no aortic complication. The effects of sudden change from the lying to the standing position in producing syncope have already been mentioned (p. 205), and when the patient is allowed to sit up he should be helped up slowly and with care. A change from the lying to the standing position by the patient getting out of bed is, of course, still more dangerous than simply sitting up in bed, and the most dangerous thing of all is for him to get up for the purpose of micturition. The reason of this has been already explained (p. 264).

Such strict precautions are, of course, not required excepting when the cardiac tonics have to be given in full doses. But when it is necessary to do this they should on no account be neglected.

As digitalis is cumulative in its action, it is often advisable after continuing it for several days to leave it off for a day or two, and then recommence; and this is a useful precaution when giving digitalis to out-patients who are seen at an interval of a week or more, even when the dose is comparatively small. Another difficulty in the administration of cardiac tonics is the gastric disturbance, loss of appetite, and vomiting which they are apt to produce.

In cases where the arterial tension is already abnormally high—e.g. in cases of contracting kidney—and the heart seems unable to drive the blood into the aorta, the proper treatment, of course, is to reduce the abnormally high blood-pressure by purgatives, diuretics, and diaphoretics, and not to attempt to strengthen the heart by the use of cardiac tonics. If this be done the pressure may be raised still further and burst the vessels, giving rise to apoplexy.

Vascular Tonics.

Vascular tonics are substances which cause increased contraction of the arterioles or capillaries. They not only raise the blood-pressure, but influence to a considerable extent the quantity of lymph poured out into the tissues or absorbed from them, and thus modify tissue change. They are of special importance in the treatment of dropsy.

The most important vascular tonics are:—

Digitalis.
Iron.
Strychnine.

Pathology of Dropsy.—Dropsy consists in the accumulation of lymph, either in small lymph spaces in the tissues (œdema, anasarca) or large serous cavities (ascites, pleural or pericardial effusions). The accumulation is caused by more lymph being poured out from the capillaries than can be removed by the lymphatics and veins.

The chief causes of dropsy are—(1) Diminished removal of lymph from the lymph spaces or serous cavities. This may be

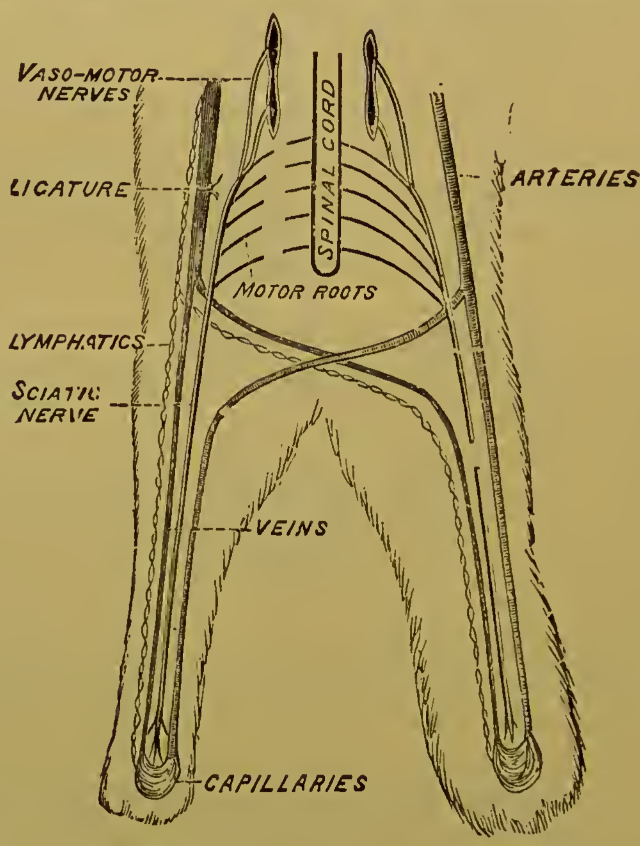

FIG. 119.—Diagram of Ranvier's experiment on dropsy. The vena cava is ligatured, and in the left leg the trunk of the sciatic has been divided so that both the motor and vaso-motor nerves contained in it are paralysed. On the right side the motor roots of the sciatic alone are divided and the vaso-motor left uninjured. There is thus motor paralysis on both sides, but vaso-motor paralysis and dropsy only on the left side.

due to (*a*) obstruction of the veins, or (*b*) of the lymphatics. (2) Increased exudation of lymph from the capillaries. This increased exudation may be due to (*a*) changes in the walls of the capillaries themselves rendering them more permeable. This appears to be the only condition which by itself can produce œdema. There are two others, however, which, although by themselves incapable of producing œdema, yet, along with others, are of the utmost

importance; these are (*b*) a watery condition of the blood, and (*c*) vaso-motor paralysis. In many, indeed in most cases of dropsy, two or three of these factors are combined.

Obstruction to the veins, or lymphatics alone, will rarely cause dropsy, unless at the same time there is increased transudation from the capillaries. Thus Ranvier found that ligaturing the vena cava of a dog did not produce dropsy in the legs, the lymph being removed either by the collateral venous circulation or by the lymphatics. On dividing the sciatic nerve on one side, however, after ligature of the vena cava, dropsy appeared in the corresponding leg, while it remained absent from the other. He showed that the dropsy was caused by paralysis of the vaso-motor, and not of the motor fibres contained in the sciatic, by dividing the motor roots of the sciatic on the other side, leaving the vaso-motor roots uninjured. When this was done motor paralysis occurred equally in both legs, but dropsy only appeared in the one where the vaso-motor nerves had been divided (Fig. 119). This experiment shows what an important factor the loss of vascular tone is in the production of œdema, and we may legitimately infer from it that vascular tonics, by increasing the contractility of the vessels, will tend to prevent œdema, or remove it when it is already present.

A watery condition of the blood does not of itself increase the exudation of lymph, nor does it produce œdema, yet in cases of anæmia or chlorosis we very frequently find a tendency to œdema of the ankles, and experiments in Cohnheim's laboratory have shown that, although a watery condition of the blood alone causes no increased exudation of lymph so long as the vaso-motor nerves are intact, yet it does so to a very great extent when the vaso-motor nerves are paralysed.[1]

Alteration of the capillaries by inflammation causes increased exudation of lymph, and tends to produce a local œdema. This œdema is greatly increased if the vaso-motor nerves are paralysed, not only attaining a much greater extent, but appearing more quickly and lasting longer. I have already mentioned that, in experiments on artificial circulation, acids added to the circulating fluid not only caused dilatation of the vessels, but increased transudation through them, and tended to render the tissues œdematous. It is not improbable that some alterations of the blood-vessels of the living body which tend to render them more permeable may be connected with imperfect oxidation and the formation of sarco-lactic instead of carbonic acid.

Arsenic has this power of lessening oxidation,[2] and it seems not improbable that the tendency to produce œdema of the eyelids which it possesses may be due to this peculiar action.

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[1] Jankowski, *Virchow's Archiv*, xciii. p. 259.
[2] Feitelberg, *Inaug. Diss.* Dorpat, 1883.

It is evident that whatever tends to increase oxidation will have an opposite effect, and will tend to prevent any excessive exudation from the capillaries. In cases of anæmia iron is therefore serviceable, and as the condition of the blood improves the tendency to œdema disappears.

What has just been said regarding the action of acids may seem to be in contradiction to the usually received opinion that the mineral acids act as vascular tonics. It is quite true that small doses of dilute acids, especially when given, as they usually are, along with bitters, frequently impart a feeling of strength and tone, whereas alkalies are frequently felt to be depressing, but in the case of both these classes of remedies this effect is probably not due to any direct action on the vessels themselves (*vide* Acids).

Cardiac Sedatives.

Cardiac sedatives are substances which lessen the force and frequency of the heart's action.

They are chiefly used, either for the purpose of lessening violent action or palpitation of the heart, or of rendering the pulse slower in febrile conditions, especially those consequent on local inflammation. It has already been mentioned that belladonna diminishes the sensibility of the heart to changes of pressure, and that sometimes it is useful in palpitation consequent on cardiac strain. Simple pressure over the cardiac region appears to have the power of lessening palpitation, so that when this occurs in consequence of any sudden emotion, there is a natural tendency to press the hand over the region of the heart. It is impossible to say whether the relief which such pressure certainly affords is simply mechanical, or is due to reflex action on the heart through the cutaneous nerves. Plasters applied to the cardiac region have a beneficial action upon palpitation similar to that of the hand, and one of the most commonly used and beneficial is belladonna plaster. In irritable-heart of soldiers Dr. Da Costa found digitalis better than any other remedy.[1]

In palpitation depending on indigestion, hydrocyanic acid is useful. In palpitation due to aortic disease, senega has been recommended. It is probable that its efficacy depends upon the diminished action of the cardiac ganglia and muscle which its active principle, saponine, produces.

An active circulation of blood is usually advantageous both for functional activity and for the repair of damage to an organ, but sometimes it may become excessive, and relief may be afforded by diminishing it (*vide* p. 342).

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[1] *Amer. Journ. Med. Sci.*, Jan. 1871.

The chief cardiac sedatives employed for this purpose are :—

Aconite.
Veratrum viride.
Antimonial preparations.

It is questionable whether in extensive inflammation of internal organs cardiac sedatives are of much service or not. They seem, however, to give relief in the feverish condition which accompanies more limited inflammation, such as tonsillitis, otitis, &c. In such cases the tincture of aconite is best employed in very small doses (one drop) frequently repeated. The introduction of this method of using the drug in divided doses is due in great measure to Ringer, and it has the very great advantage that the desired effect can be produced with greater certainty and with less risk of an overdose being given.

Vascular Sedatives.

Vascular sedatives are substances which, by increasing the contraction of the vessels, lessen the flow of blood through them. They are chiefly used to lessen local inflammation or prevent hæmorrhage. One of the most powerful of all vascular sedatives is cold. For its use in local inflammation *vide* p. 343. It is not only a vascular but a cardiac sedative, and **ice** swallowed in considerable quantity will tend to lessen the action of the heart. It is therefore one of the means to which we chiefly trust in cases of hæmoptysis. In hæmatemesis it has the double action of lessening the activity of the heart, and of contracting the vessels in the stomach.

The remedies which are chiefly employed in addition to cold are :—

Digitalis.
Ergot.
Hamamelis.
Lead acetate.
Opium.

CHAPTER XII.

REMEDIES ACTING ON THE SURFACE OF THE BODY.

Irritants and Counter-irritants.

Irritants are substances which, when applied to the skin, cause a greater or less degree of vascular excitement or inflammation. They are employed for the sake of their **local action**, to produce increased circulation in the part to which they are applied, and thus to remove abnormal conditions already present in it.

When irritants are employed for the purpose of affecting reflexly a part **remote** from the seat of application they are named **Counter-irritants.**

Irritants are subdivided, according to the amount of effect produced, into rubefacients, vesicants, pustulants, and escharotics.

Rubefacients produce simply congestion and redness, which may be merely temporary, passing off in a few minutes, or may be more permanent, remaining for several days.

When more powerful, so as to cause exudation between the true skin and epidermis, giving rise to vesicles, they are called **vesicants,** or **epispastics.**

When they do not affect the whole skin alike, but do so unequally, and irritate isolated parts in it, such as the orifices of the sudoriferous glands, so powerfully as to give rise to pustules, they are called **pustulants.**

When they destroy the tissues altogether, forming a slough, they are called **caustics** or **escharotics.**

The difference between these sub-classes is chiefly one of degree, and not of kind. The weaker ones produce the higher degrees of action when applied for a long time, and the stronger ones produce the slighter kinds of action when applied for a short time.

It must be remembered that, although inflammation is usually associated with increased circulation, the two things are essentially different.

Inflammation is the injury to the tissue; the increased circulation is the attempt to repair it.

Increased circulation occurs wherever we have increased

functional activity, whether this be for the purpose of performing a normal function, as in glands during the process of secreting, and in muscles during contraction, or for the purpose of **repair.** When repair is going on slowly, the process may be frequently quickened by increasing the supply of blood to the part, and this is the reason for using friction, and liniments and blisters of various kinds, in cases of **chronic inflammation** in joints or in ulcers.

Sometimes irritation fails to cause absorption, from being too weak. In a case of rheumatic gout which I saw some years ago, irritating liniments had been applied for some time in vain, until, by mistake on the patient's part, so much iodine liniment was put on at once as to cause vesication over the whole back of the hand, when recovery began immediately.

In **acute inflammation,** however, the greatly increased circulation, along with the heightened sensibility of the sensory nerves in the inflamed part, causes much pain, and this is relieved when the tension of the blood in the inflamed part is lessened. We notice this very clearly when the finger is inflamed in consequence of a prick from a thorn, a bruise, or other injury. When it is allowed to hang by the side, the throbs of pain, coincident with every pulse-beat, become excruciating, while, if raised above the

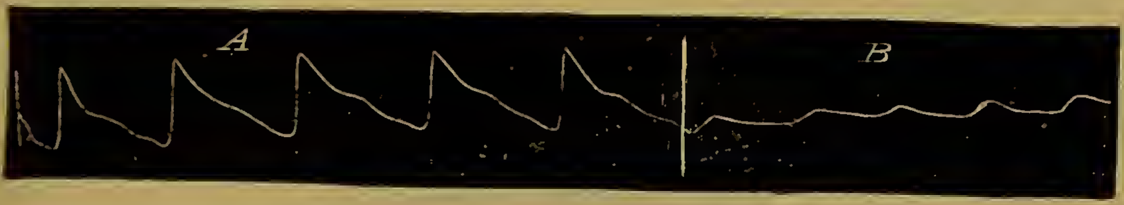

FIG. 120.—Tracings from the radial artery at the wrist : *A* before and *B* after the application of a cloth dipped in cold water round the arm. (After Winternitz.)

head, so that the pressure of blood in the vessels is less, the pain becomes greatly diminished. The tension in the vessels may be relieved likewise by causing contraction of the arteries leading to the part by a cold compress around the arm (Fig. 120), or by dipping the finger in cold water; but relief is also afforded by a warm poultice applied to the finger. At first sight it seems strange that **heat** and **cold** should both relieve the pain, but a little consideration will show that they both relieve the tension in the vessels of the inflamed part. Cold does so by causing a reflex contraction of the afferent arteries, and thus diminishing the quantity of blood going to the inflamed part. Warmth, on the other hand, dilates the capillaries of the collateral circulation, and thus diverts the current away from the inflamed vessels.

The use of **counter-irritation** as a remedial measure depends on the fact that similar alterations to those produced by heat and cold on the finger may be produced on the circulation in internal organs reflexly through the nervous system.

When an **irritant** is applied to any part of the skin, it causes

a local dilatation of the vessels and redness of that part, but contraction of the vessels in other parts of the body. Probably this contraction takes place with the greatest force in certain organs having a definite nervous relation to that part of the surface

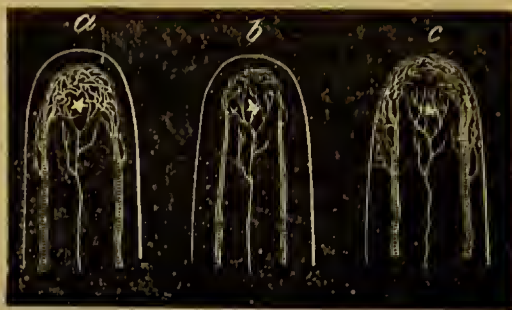

FIG. 121.—Diagram to show the effects of heat and cold in lessening the pain of inflammation. The diagram is supposed to represent the end of the finger. The small star indicates the point of irritation, e.g. a prick by a thorn. The line in the centre of each figure is intended to represent the nerve going to the injured part; and at the side of each figure is an artery and vein connected by a capillary network. In *a* the capillary network around the seat of irritation is seen to be much congested; the nerve-filaments are thus pressed upon and pain is occasioned. *b* represents the condition of the finger after the application of cold to the arm or hand. In consequence of the contraction of the afferent arteries the finger becomes anæmic; no pressure is exerted on the nervous filaments, and pain is alleviated. *c* represents the finger after it has been encased in a warm poultice; the capillary network at the surface of the finger is dilated, and the blood is thus drawn away from the seat of irritation and the pain therefore relieved.

which is irritated. Zülzer found that when cantharides-collodion was painted repeatedly over the back of a rabbit for fourteen days, the vessels underneath the skin, and the superficial layers of

FIG. 122.—Diagram to show congestion of the lung. The pulmonary vessels are shown dilated, and those of the thoracic wall contracted.

muscles, were congested. The deeper layers of the muscles, the thoracic wall, and even the lung itself, were much paler and more anæmic than those of the other side.

It is probable that a similar condition occurs in man, and that when we apply a blister to the side we, sometimes at least, cause contraction of the vessels in the pleura and lung below, and thus relieve pain in the chest in much the same way as when we apply cold to an inflamed finger. It has been supposed that the action of a poultice or blister was simply to draw away blood from the

inflamed part. We have seen that the poultice does this in the case of an inflamed finger, but in an inflamed lung or pleura the quantity which comes to the skin is insufficient to explain the relief. It is quite possible, however, that the vessels in the lung and pleura adjoining the inflamed district may be dilated by the application of a poultice or blister to the side, and thus relief is afforded in the same way as by the application of a poultice to the finger. It is not easy to say in which of these ways a poultice or

FIG. 123.—Diagram to explain the action of counter-irritation. A blister or other counter-irritant is shown applied to the chest-wall. The stimulus which it causes is transmitted up the afferent nerves to the vaso-motor centre; it is thence reflected down the vaso-motor nerves to the pulmonary vessels, causing them to contract, while it is reflected down vaso-dilating fibres to the vessels of the thoracic wall and probably of other parts of the body also, causing them to dilate, and thus lessening the pulmonary congestion by withdrawing blood from the lungs. (Compare with Fig. 122.)

blister acts in any particular case. Clinical experience seems to show that sometimes the blisters relieve acute inflammation by causing contraction of the afferent vessels (as represented in the accompanying diagram, Fig. 123) and thus lessening the tension in the vessels of the inflamed part. If the blister is too near to the inflamed part, it may increase instead of diminishing the congestion, and thus do harm instead of good.

As a matter of practice, the rule is usually insisted upon, that in a case of pericarditis, for instance, the blister should not be put immediately over the pericardium, but at some little distance from it.

Counter-irritation is not only used, however, as a means of lessening congestion and pain in acute inflammation, it is also employed with much advantage to cause the re-absorption of inflammatory products. The use of the increased circulation which a blister causes in a chronic ulcer is unquestionable, and the rapid absorption of the thickened margins of the ulcer is perceptible to the eye. A similar absorption appears to occur in deeper-seated organs, such as the lung, on the application of counter-irritation to the chest, and painting with iodine liniment is useful in promoting absorption of liquid effused into the pleural cavity or of the product of chronic inflammation of the lung. The mode in which the irritation acts is probably the same both in the chronic

ulcer and in the lung, i.e. by increasing the circulation through the part affected. Where the blister is applied, as in acute pericarditis, to lessen congestion, it is usually placed at a little distance from the inflamed part, but where we wish to increase absorption, as in consolidation of a part of the lung, we apply the counter-irritant directly over the consolidated part.

Rubefacients.

Mechanical, as friction.
Ammonia.—Solution of ammonia, compound camphor liniment.
Alcohol (prevented from evaporating by oil-silk or a watch-glass).
Arnica.
Cajeput oil.
Camphor.
Capsicum.
Chloroform (prevented from evaporating, like alcohol); chloroform liniment.
Ether (like chloroform).
Iodine and its preparations.—Iodide of cadmium, iodide of lead.
Menthol.
Mustard.
Oil of turpentine, of nutmeg, and many other volatile oils.

Vesicants.

Acetic acid (glacial).
Heat of:
 Boiling water.
 Corrigan's hammer.
Cantharides.—Solutions, plaster, cantharidin.
Euphorbium.
Mezereon.
Volatile oil of mustard.
Rhus toxicodendron.

Pustulants.

Croton oil.
Tartarated antimony.

Caustics.

Actual cautery.
Acids:—Acetic (glacial).
 Carbolic.
 Chromic.
 Hydrochloric.
 Lactic.
 Nitric.
 Osmic.
 Sulphuric.
Alkalies:—
 Lime.
 London paste (p. 346).
 Vienna paste (p. 346).
 Potash.
 Soda.
 Ethylate of sodium.
 Alum (burnt).
Antimony (chloride).
Arsenic.
Bromine.
Soluble compounds of the heavier metals; as:
 Copper sulphate.
 Mercuric chloride.
 ,, nitrate.
 Silver nitrate.
 Zinc chloride.
 Zinc sulphate.

Rubefacients.— One of the simplest rubefacients is mere **friction.** This may be made either with the hand, or more effectually still, with a rough cloth or a flesh-brush. Friction also greatly aids the action of many of the slighter rubefacients.

Rubefacients may be used for their action upon the skin itself

to relieve itching. They may also be used for their effect on deeper-seated structures.

Friction, with firm pressure, is used in shampooing. Upward friction in the limbs will diminish the tension in dropsy, by removing part of the fluid from them. It also aids the circulation of the lymph, and by accelerating the passage of the products of muscular waste from the muscles themselves into the general circulation, it removes to a great extent the sense of fatigue after over-exertion (p. 131). When applied along the back it soothes conditions of nervous excitement, and tends to produce sleep. Friction, along with stimulating liniments, applied to the joints after active inflammation has subsided in them, tends to remove the swelling and to restore their function.

Neuralgic pains are frequently relieved by the application of rubefacients such as ammonia, chloroform applied by a watch-glass, or a mustard-plaster to the painful spot.

Conditions of nervous debility are sometimes benefited by mustard liniment applied over the spine, and a mustard-plaster to the nape of the neck is sometimes useful in nervous irritability with sleeplessness. In addition to the action which the mustard has on the vessels, it produces a sharp pain, so that it is employed also to rouse persons suffering from narcotic poisoning, or from coma.

Mustard-leaves or iodine liniment applied over consolidated parts of the lung tend to cause absorption of inflammatory products, and are used for this purpose in cases of effusion into the pleura or pericardium, of chronic consolidation remaining after an attack of pleurisy or pneumonia, or in commencing phthisis.

Vesicants.—Vesicants are employed locally in **chronic ulcers** and to cause absorption of effusions into **joints,** or chronic thickening about them. When applied around the inflamed joints in acute rheumatism, they not only relieve the local affection, but appear to have a curative action on the general febrile condition.

In neuralgia, blisters over the painful point are useful, and sometimes, when neuralgia is in the side, or in the breast, it may be relieved by applying the blister over the corresponding part of the spine where there is usually a spot which is tender on pressure. In sciatica, the relief is often greater when the blister is applied to the heel, than over the nerve itself.

In neuralgia also it not unfrequently happens that a slight application of the actual cautery is more efficacious than a blister. The most convenient form of this is Paquelin's thermocautery.

In inflammation of the pericardium or pleura, a blister frequently relieves the pain, and it sometimes lessens or cuts short the inflammation. Applied over the epigastrium, blisters relieve vomiting arising from various causes.

In cerebral affections, such as obstinate headache, in menin-

gitis and hydrocephalus, blisters to the nape of the neck or under the mastoid process are useful.

Hysterical paralysis of the limbs sometimes yields to blisters locally applied; and hysterical aphonia is sometimes removed by a blister over the larynx.

Pustulants.—Pustulants are employed for the purpose of keeping up a continuous moderate irritation in chronic inflammations: tartar emetic ointment, and croton-oil liniment, seem sometimes to be of considerable advantage in chronic inflammation of joints or synovial membranes, in chronic bronchitis and in pleurisy; perhaps sometimes in phthisis. They have been used also as an application to the spine in paralysis and hysteria, and to the head in tubercular meningitis, and to the nape of the neck in chronic headache or giddiness. They were much employed formerly, but of late years iodine liniment or small blisters have to a great extent taken their place.

Caustics.—Caustics are used to destroy excrescences on the surface of the skin and mucous membranes: warts, condylomata, or polypi; to destroy exuberant and unhealthy granulations in ulcers and fungating sores: thus, a slight touch with nitrate of silver, sulphate of copper, or with nitric acid, will sometimes cause the tissues in an unhealthy wound after an operation to become less exuberant, and take on a healthy healing action.

Caustics may be used to destroy malignant growths. Generally a surgical operation is preferable for this purpose, but sometimes patients have such a horror of the knife that they will not submit to an operation, and in such cases caustics are occasionally employed. For this purpose one of the following may be applied: Vienna paste consisting of caustic potash and caustic lime moistened with water, or London paste, which consists of caustic soda and lime moistened with alcohol. Sulphuric acid mixed with sawdust has sometimes also been used, but it is exceedingly painful. Arsenious acid made with various inert substances into a paste is not unfrequently employed with considerable success by charlatans, who sometimes succeed in removing cancerous growths by its application in apparently hopeless cases, but the risk attending its use is considerable.

Caustics are sometimes employed also to open abscesses, especially abscesses of the liver, if it is thought advisable to cause adhesions between the viscus and the abdominal wall before the abscess is opened, so as to avoid any risk of pus finding its way into the abdominal cavity. The substance usually employed for this purpose is caustic potash.

Caustics are also used to keep up chronic irritation, as in chronic headache or epilepsy, a wound being first made by the use of the caustic, and prevented from healing by the introduction of a foreign body into it, or by the continued application of some irritating ointment, such as savine ointment.

Caustics are also used as an application to the bites of venomous serpents, or of rabid dogs, in order to destroy the virus and prevent its general action on the organism. The weaker caustics are of no use for this purpose. I have seen a boy die of hydrophobia six weeks after he was bitten by a mad dog, although the wound had been thoroughly cauterised by nitrate of silver five minutes after the bite. In all cases the parts around the bite should be, if possible, excised and then cauterised with a red-hot iron, a ligature being, if possible, placed between the bitten part and the heart until the operation has been effected, so as to prevent any absorption of the virus.

Emollients and Demulcents.

Emollients are substances which soften and relax, while **Demulcents** are substances which protect and soothe the parts to which they are applied.

Many substances exercise both of these actions, and so no very sharp line of distinction is drawn between them. Emollients, however, are more generally spoken of in relation to their application to the skin, and demulcents to the mucous membranes.

Demulcents.

- Bread.
- Collodion.
- Cotton-wool (for external use only).
- Figs.
- Fuller's earth.
- Gelatine.
- Iceland moss.
- Isinglass.
- Glycerin.
- Gum.
- Honey.
- Linseed.
- Linseed-tea.
- Marsh-mallows.
- Almond-oil.
- Olive-oil.
- Starch.
- White of egg.

Emollients.

- Moist warmth—bathing with warm water, hot sponge, hot fomentations, steam.
- Poultices made of substances which retain heat and moisture—bran, bread, figs, flour, linseed-meal, oatmeal, &c.
- Gelatinous substances.
- Fats—almond-oil, glycerin, lard, linseed-oil, neat's-foot oil, olive-oil, spermaceti, suet, lanolin.
- Paraffin—petrolatum, vaseline, and unguentum petrolei.
- Soap and other liniments.

The Action of Demulcents is chiefly mechanical. They form a smooth, soft coating to an inflamed mucous membrane, or to a skin deprived of its epidermis, and they thus protect the surface from external irritation, and allow the process of repair

to go on. They are used externally in cases of irritating skin diseases, where the epidermis from one cause or another has been broken or removed, as by friction, exposure to cold, &c. Internally they are employed when the mucous membranes have been irritated, as, for example, in the after-treatment of cases of irritant poisoning.

Mucilaginous substances are also used to relieve pain and irritation in the throat, and to lessen the irritable cough which frequently depends on congestion of the pharynx and upper parts of the respiratory passages.

Such substances as figs, prunes, and even cabbage, are employed to protect the intestines from injury by hard and pointed substances which have been accidentally swallowed. They do this by leaving a bulky indigestible residue in which the pointed article becomes embedded, and thus passes along the intestine without lacerating it.

The Action of Emollients is to relieve the tension and pain in inflamed parts; **warmth** and **moisture** do this by dilating the collateral blood-vessels in the manner already described (p. 342). They also relax the tissues themselves and lessen the pressure upon the nerves of the part.

Fatty emollients soften the skin and thus render it softer and more flexible. These emollients also aid the immediate effect of friction upon the skin, enabling it to be applied with greater advantage, and to act on the more deeply-seated tissues, as, for example, in cases of stiffness in joints.

Therapeutic Uses.—Warmth and moisture are almost invariably used to relieve spasm and the pain attending it, as well as to relieve pain in all cases of inflammation, whether superficial or deep-seated, and they relieve so much that, with many people, the connection between pain and poultice has come to be a household word. When poultices are intended to act directly on the part to which they are applied, the linseed, bran, or bread should be applied to the skin with nothing between, or at most with only a thin piece of muslin, but when intended to act on deep-seated organs, a considerable thickness of flannel should be interposed, so that the heat may come gradually through, and allow an excessively hot poultice to be applied without burning the skin.

In cases of disease of the respiratory passages the warmth is usually applied by means of **inhalation.**

Fatty emollients, by softening the skin or mucous membranes, such as those of the lips, prevent them from cracking, and are used by persons with a delicate skin to prevent cracks forming on exposure to cold.

They are also used to prevent friction between surfaces of skin constantly in contact, as between the nates and inner joints in children, and to prevent bed-sores.

Astringents.

These are substances which cause contraction of the tissues to which they are applied and lessen secretion from mucous membranes.

- Acids.
- Alcohol.
- Alum.
- Chalk and Lime.
- Salts of the heavier metals, e.g.—
  - Bismuth subnitrate, &c.
  - Cadmium sulphate.
  - Copper sulphate.
  - Ferric chloride.
  - Lead acetate.
  - Silver nitrate.
  - Zinc sulphate.
- Gallic acid.
- Tannic acid.
- Vegetable substances containing these acids, e.g.—
  - Catechu.
  - Galls.
  - Kino.
  - Oak-bark.
  - Uva-Ursi.
  - Arbutin.

Astringents are usually divided into local and remote.

Local astringents are those which affect the part to which they are applied. **Remote** are those which act on internal organs after their absorption into the blood.

With the exception of gallic acid and ergot they all **coagulate** or precipitate **albumen.** Dilute mineral acids do not coagulate albumen, but precipitate albuminous substances from the alkaline fluids in which they are naturally dissolved in the body.

When applied to a surface from which the epidermis has been removed, the other astringents combine with the albuminous juices which moisten this surface, as well as with the tissues themselves, and form a pellicle more or less thick and dense, which in some measure protects the structures beneath it from external irritation, at the same time that they cause the structures themselves to become smaller and more dense. On a mucous membrane they have a similar action, and they lessen its secretion. It was formerly supposed that their action was partly due to their causing the blood-vessels going to a part of the body to contract, thus lessening the supply of fluid to it, as well as to their effect on the tissues themselves. But experiment has shown that, while nitrate of silver and acetate of lead possess this power, perchloride of iron and alum do not, and that tannic and gallic acids actually dilate the vessels. The astringent action of these latter drugs must therefore be exerted upon the tissues. (Rossbach.)

Uses.—Astringents may be employed **locally** in various forms. In the solid form, as a powder, or in various prepara-

tions, such as lotions, ointments, plasters, glycerines, &c., they are applied, especially the metallic astringents, to wounds and ulcers for the purpose of reducing the size and increasing the firmness of exuberant granulations, as well as of protecting the surface by forming a pellicle over it. They are used to lessen congestion and diminish the secretion of the various mucous membranes—as a lotion to the eye and mouth; as a gargle or a spray to the throat; in the form of an injection to the nose, urethra, and vagina; and of suppositories to the rectum. Administered internally, several astringents have a powerful effect in checking diarrhœa, and certain of them may have a local action upon the stomach and intestines.

The **remote** action of such astringents as acetate of lead and gallic acid, when absorbed into the blood, in lessening **hæmorrhage**, is made available in the treatment of hæmoptysis, hæmatemesis, hæmaturia, and loss of blood from other parts of the body.

Styptics.

Styptics are substances which arrest the flow of blood from broken or wounded surfaces or vessels. They may do this either by aiding the rapid formation of a coagulum which will plug up the wounded vessels, or by causing the vessels themselves to contract so much as to check the flow of blood out of them. They are closely connected with astringents, which, as we have already mentioned, nearly all coagulate albuminous substances.

Acids.	Collodion, Matico, Spider's-web, } acting mechanically.
Actual cautery.	
Alum.	
Ferric chloride.	
Tannin.	
Lead acetate.	

Substances acting on the blood-vessels:—

Cold (Ice).
Digitalis.
Ergot.

Action.—Matico and cobwebs act **mechanically** in aiding the formation of a clot around the fibres. Collodion also acts mechanically by exerting pressure over the surface, and thus preventing the blood from issuing.

Alum, lead acetate, and ferric chloride cause **coagulation** of the blood.

Pressure to the surface, cold sponges or ice, cause the vessels to **contract**, and thus prevent the blood from running out of them in superficial hæmorrhage.

Lead acetate and gallic acid, when absorbed into the blood,

not only tend to lessen secretion from the mucous membranes, but arrest hæmorrhage from internal organs. This is probably partly due to their effect in increasing the coagulability of the blood, and possibly partly also to their power of causing contraction of the arterioles. Ergot and digitalis also lessen or arrest hæmorrhage, although they have little or no action on coagulation, and their action probably depends on their power to cause contraction of the arterioles.

A dependent position increases the pressure of blood locally in the part, and thus tends to increase hæmorrhage. It is therefore advisable to keep the bleeding part as much raised as possible.

Powerful action of the heart tends to increase the blood-pressure generally. In cases of severe hæmorrhage it is therefore of the greatest importance that the patient should keep **absolutely quiet,** and that all the food should be taken cold.

Cold to the surface is a powerful agent in checking internal as well as superficial hæmorrhage. It probably acts by causing reflex contraction of the vessels (compare Rossbach's experiments, p. 252). A cold key to the back of the neck and cold water to the nose are frequently useful in epistaxis, and ice-bags to the chest or epigastrium are useful in hæmoptysis and hæmatemesis. It is probable that other stimuli to the surface act on the vessels in a similar way, and probably this is the explanation of the fact that menorrhagia and metrorrhagia are sometimes successfully treated by placing a plug of cotton wool soaked in a mixture of vinegar and brandy in the vagina, or applying the same mixture either on cotton wool or on a napkin to the vulva.

The powerful action of hot water injected into the vagina and uterus in arresting *post partum* hæmorrhage (p. 455) is probably due partly to its causing a reflex contraction of the vessels and of the uterus itself, and probably also to its direct stimulating action on the muscular walls of the uterus.

CHAPTER XIII.

ACTION OF DRUGS ON THE DIGESTIVE SYSTEM.

ACTION OF DRUGS ON THE TEETH.

Although the hurry and bustle of modern life is apt to make people forget it, mastication is a most important part of the digestive process. During early life the stomach and intestines may be able to digest imperfectly-masticated food, but as years advance they cease to do so, and imperfect mastication becomes a fruitful source of dyspepsia.

If the teeth are entirely or almost entirely gone, the person may chew with his gums, but if they are only partially gone it frequently happens that those which remain oppose one another only sufficiently to prevent the gums from closing, while they do not help mastication.

The decay of teeth is chiefly due to the dentine being attacked by the acid products of the decomposition of food in the mouth. This decomposition is to a great extent due to bacteria, and antiseptics are therefore useful in preventing decay.

By cleaning the teeth with a soft brush at night before going to bed, particles of food sticking between them may be removed, and thus its decomposition and consequent injurious action on the teeth may be avoided. Chalk is employed as a basis of most dentifrices, as its mechanical action is sufficient to clean the teeth without injuring their polish, and at the same time it neutralises any acid which may be present. Charcoal has also a useful mechanical action greater than that of chalk, but it is more liable to scratch the enamel.

The antiseptics which are usually employed to cleanse the teeth are borax, quinine, and carbolic acid. Dilute solutions of permanganate of potassium are also very useful, but have a very disagreeable taste. Where the gums are soft and spongy and are apt to leave the fang of the tooth more or less exposed, vegetable astringents, such as areca nut, catechu, kino, and rhatany are useful. Mineral acids when given medicinally cause an unpleasant feeling of the teeth being on edge, and are also injurious to the teeth; they are therefore usually sucked up by means of a glass tube or quill, instead of being simply swallowed. When used as gargles for the throat, their injurious action on the teeth

may be to a considerable extent prevented by previously rubbing the teeth with oil, butter, or lard, and washing out the mouth or brushing the teeth with a weak solution of alkaline bicarbonate or soap. Soluble preparations of iron, especially persalts, are apt to stain the teeth, and they are therefore also given by means of a tube; alum appears also to have a very injurious action on the teeth; alum gargles should therefore not be employed for a length of time together, and the same precautions should be used as with acid gargles.

When the gums have receded somewhat from the crown of the teeth, pain or a soreness is not unfrequently felt in the teeth, although no definite caries is present. This soreness appears to be due to the irritant action of acid secretions in the mouth upon the exposed fang, and it may be often to a great extent removed by washing the mouth out with a weak solution of bicarbonate of sodium, or rubbing finely-powdered chalk or magnesia along the gums. When toothache occurs in consequence of caries, it may sometimes also be relieved by holding some brandy in the mouth, or by placing a small pledget of cotton-wool dipped in tincture or liquid extract of opium with a little bicarbonate of sodium in the cavity of the tooth. A pledget of cotton-wool dipped in creasote or oil of cloves is often used for a similar purpose, and one of the most effectual remedies is to dip a small pledget of cotton-wool in pure carbolic acid liquefied by heat, and place it in the cavity of the tooth, taking care to cover it well with clean cotton-wool so as to prevent the carbolic acid coming in contact with the tongue or cheeks. Chlorate of potassium often lessens toothache if due to inflammation of a large open carious cavity. Phosphate of calcium frequently relieves toothache occurring during pregnancy or lactation and is sometimes useful also in toothache unconnected with either of these conditions.

ACTION OF DRUGS ON THE SALIVARY GLANDS.

Sialagogues.

These are remedies which **increase** the secretion of **saliva**.

Anything which is chewed, or even turned about in the mouth, such as a pebble, will increase the secretion of saliva; but the chief sialagogues have a stimulating action of their own.

Action.—In the secretion of saliva there are **two factors**—first, the activity of the **secreting cells**; secondly, the supply of new material to them, from which they may manufacture the secretion. This depends on the **circulation**.

Secreting cells do not derive the new material from which they form the secretion directly from the blood. They obtain it from the lymph which fills the adjacent lymph-spaces. Hence they may continue to secrete for a short while after the circula-

tion has ceased, as in the sweat-glands of an amputated limb, or in the salivary glands after the head of the animal has been separated from the body. But the supply of lymph soon becomes exhausted unless a supply of fresh lymph in the spaces is kept up by exudation from the blood-vessels. We therefore find that abundant secretion is usually, though not invariably, associated with an abundant blood-supply. If the flow of blood is not rapid the secretion must soon diminish or come to a stop, for, although it may occur rapidly at first, the lymph which has accumulated in the lymph-spaces supplying the cells soon becomes exhausted.

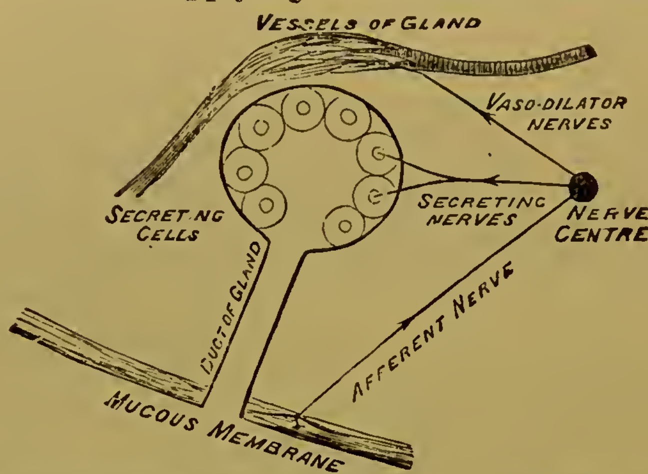

FIG. 124.—Diagram representing the general relation of nerves to the secreting cells and vessels of a gland. For the sake of simplicity only one afferent nerve and one nerve-centre and one set of secreting and vascular nerves are here represented.

In the salivary gland, when the secretion is going on, the arteries usually dilate, and the blood flows rapidly through them. The submaxillary gland, in which secretion has been best studied, appears to receive four kinds of nerves—two sets being contained in the chorda tympani and two in the sympathetic.

The chorda contains some fibres which act on the blood-vessels, causing them to dilate and allow the blood to flow freely through the gland, and others which stimulate the cells of the gland to secrete a thin, watery saliva. These two kinds are spoken of as vaso-dilating and secreting, or secretory, fibres (Fig. 124).

At present the usually accepted theory is that the secretory nerves have a direct influence upon the tissue-change in the cells of the gland. During secretion the granules in the cell decrease in number and generally in size, the hyaline substance increases, and the network within the cell grows.[1] It is not at all improbable, however, that in addition to their action upon secreting nerves some drugs influence the amount of fluid poured out from the vessels. For if we inject a solution of quinine into the duct of the gland and thus destroy its secreting power, and afterwards irritate the chorda tympani, the lymph poured out from the blood-vessels will accumulate in the gland and render it œdema-

[1] Langley, *Proc. Camb. Phil. Soc.*, Nov. 12, 1883.

tous; but if an animal be poisoned with atropine the gland does not become œdematous when the chorda tympani is stimulated—although the blood-vessels going to it are dilated and its power of secretion is completely destroyed. We might suppose that the gland did not become œdematous because the lymph, although not used up by the gland, had been carried away by the cervical lymphatics. But this is not the case, for Heidenhain has found that the flow of cervical lymph is not increased under these circumstances.

It appears to me that the circumstance can hardly be explained otherwise than by supposing that atropine not only paralyses the secreting fibres of the chorda, but acts upon the vessels in such a manner as to greatly diminish or prevent the exudation which would usually take place from them into the lymph-spaces on irritation of the chorda.

The sympathetic contains some fibres which cause the vessels of the gland to contract and the blood to flow slowly through it, and others which stimulate the cells to secrete a thick and viscid saliva.

Besides the ordinary secretion of saliva regulated by the action of the nerves, there is a secretion which is usually termed paralytic, because it occurs, not after irritation, but after paralysis of the nerves going to the salivary gland. It occurs in the sub-

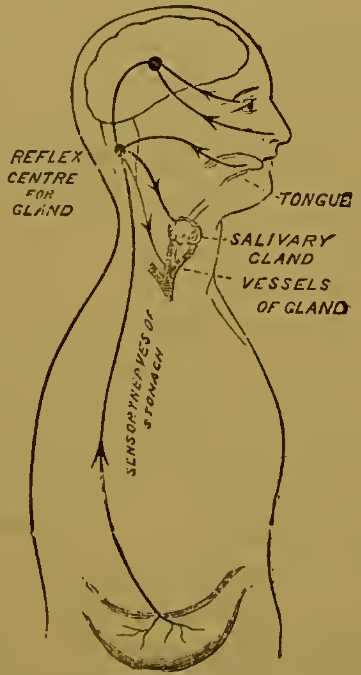

FIG. 125.—Diagram to show the afferent nerves by which the secretion of saliva may be reflexly excited.

maxillary gland, when its nerves have either been paralysed by the injection of small doses of curare into the artery going to the gland, or by a section of the combined lingual nerve and chorda tympani, or extirpation of the submaxillary ganglion. It is not improbable that morphine also, like curare, produces it, because

in moderate doses it causes dryness of the mouth, but in enormous doses causes excessive salivation.

The secretion of saliva may be stimulated by the **direct** action of drugs upon secreting nerves in the gland itself, or **reflexly** through the sensory nerves of the mouth, stomach, eye, or nose (Fig. 125). The mere smell, or sight, of appetising food, causes secretion of saliva, which is probably due to the nerves of smell and taste acting through the brain upon the medulla. The **brain**, when excited by mere recollection, may also stimulate the secretion of saliva.

Increased salivation is a common accompaniment of sickness or nausea. The afferent nerve here appears to be the gastric branches of the vagus.

The **nerve-centre** which regulates the secretion of the thin chorda-saliva is probably the nucleus of the seventh nerve situated in the medulla oblongata.

Efferent fibres pass out along the chorda tympani and reach the gland, some directly, and some after passing through the submaxillary ganglion.

The **afferent** fibres, which convey stimuli from the mouth to the medulla are contained in the lingual branch of the fifth, and the glosso-pharyngeal nerves. Those which convey stimuli from the stomach, and excite the salivation which accompanies nausea, are contained in the vagus. The salivary centre may also be stimulated by impulses sent down from the brain, and the nerves of sight and smell may act as afferent nerves to the salivary centre indirectly through the brain (Fig. 125).[1]

Besides the nerve-centre in the medulla oblongata there are **subsidiary** nerve-centres. These are the submaxillary ganglion and small ganglionic masses in the submaxillary gland itself.

Sialagogues have been divided into two **classes** : **1st, topical**, or direct ; and 2nd, specific, **remote**, or indirect. The names *direct* and *indirect* are complete misnomers, and ought not to be used ; inasmuch as the so-called *direct* sialagogues are those which act *directly* on the *mouth*, but do *not* act *directly* on the substance of the *gland*, or on the nervous structures contained within it or immediately connected with it.

Sialagogues are better divided according to their mode of action into **reflex** sialagogues, **specific** sialagogues, and those which act both reflexly and specifically, and may be called **mixed** sialagogues.

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[1] The nasal branches of the fifth nerve probably also act as afferent nerves for the salivary secretion, for I have noticed that on dipping the tip of the nose into hot water containing a little compound tincture of benzoin, salivation occurred, ceased when the nose was withdrawn, and again occurred regularly whenever the nose was again introduced into the mixture. The mere inhalation of the vapour had no effect.

Reflex Sialagogues.

Acids, mineral and vegetable.
  Acid salts.
Alkalies.
Ethereal bodies—
  Ether.
  Chloroform, &c.
Pungent substances—
  Mustard.
  Horseradish.
  Ginger.
  Pyrethrum.
  Mezereon.
  Tobacco, &c.
  Rhubarb.
  Cubebs.
  Nauseants.
    Tartar emetic, &c.

Specific Sialagogues.

Jaborandi. (Pilocarpine.)
Muscarine.
Physostigma. (Physostigmine.)
Tobacco.
Compounds of Iodine.
Mercury and its compounds.

Reflex Sialagogues.—Acids, ether, ginger, horseradish, mezereon, mustard, pyrethrum and rhubarb, all produce salivation by stimulating the salivary glands reflexly through the nerves of the mouth.

The effect produced by reflex or topical sialagogues is not the same for each. Ether and dilute acids produce a thin, watery saliva, but alkalies cause the secretion of a thicker and more viscid saliva: the former appearing to affect chiefly the chorda tympani, and the latter the sympathetic.

Nauseants, such as tartar emetic, stimulate the glands reflexly through the vagus.

Mixed Sialagogues.—Mercury probably acts partly upon the gland structures and partly reflexly through the nerves of the mouth. Tobacco, when smoked or chewed, probably acts both reflexly and specifically. Iodide of potassium may act partially as a reflex sialagogue, for it is secreted in the saliva, and it therefore comes to be present in the mouth more or less persistently. It is probable, however, that it acts also upon the gland-structures, though it has not been determined whether the secreting cells or the nerves are chiefly affected.

Specific Sialagogues.—The **peripheral ends** of the secreting nerves in the gland itself are stimulated by pilocarpine or jaborandi, muscarine, nicotine and physostigmine, so that secretion is induced by the injection of these substances into the blood even after all the nerves going to the gland have been cut.

In large doses these substances paralyse the ends of the secreting nerves, so that irritation of the chorda tympani will no longer cause secretion. Physostigmine and nicotine, besides acting on the peripheral terminations of the secretory nerves,

stimulate the **central ends** of those nerves so that section of the chorda tympani greatly lessens the secretion which these substances cause, although it may still persist from the effect of the drug upon the peripheral terminations.

The peripheral action of physostigmine and nicotine is, however, much less marked than that of muscarine and pilocarpine, so that the secretion caused by the two former after the nerves have been divided is very much less than that produced by the latter.

Physostigmine acts also on the **sympathetic nerves,** producing contraction of the vessels at the same time that it is stimulating the secreting centre in the medulla. In consequence of this double action, secretion is rapid at first; it, however, diminishes very quickly or ceases entirely, the circulation being so much lessened by the contraction of the vessels that the glands do not get sufficient supply of new material to go on secreting.

Excretion by the Saliva.

Iodide of potassium is very quickly excreted by the kidneys, so that the great bulk of it passes out of the body in a short time after it has been taken. But a little of it is retained very persistently for a length of time. There may be more than one reason for this. It is possible that it becomes combined with albuminous matters of the blood and tissues, and this combination being only slowly broken up, the elimination of the drug continues for a length of time. Another reason appears to be that it is excreted even more readily by the salivary glands than by the urine. The saliva in which it is contained is swallowed, the iodide is again absorbed from the stomach and carried by the circulation to the salivary glands. It thus goes on in a continual round from mouth to stomach and from stomach to mouth (Fig. 126). Iodide of iron, and probably other iodides, are eliminated by the saliva in the same way. Iodide of iron occurs in the saliva either when injected into the artery of the gland or when absorbed from the stomach. When lactate of iron and iodide of potassium are introduced simultaneously, or at a short interval after each other, into the stomach, so that iodide of iron is formed there by their combination, iodide of iron is found in the saliva.[1] But if they are injected separately into the blood, iodine of potassium alone without any iron appears in the saliva. Iodine probably causes other substances besides potassium and iron to appear in the saliva when they are combined with it. It probably does so to quinine, for when iodide of potassium and quinine are given together in a mixture, patients frequently

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[1] Bernard, *Physiologie Expérimentale*, tom. ii. p. 99.

complain of a very persistent bitter taste in the mouth much more marked than when the quinine is given in simple solution with acid.

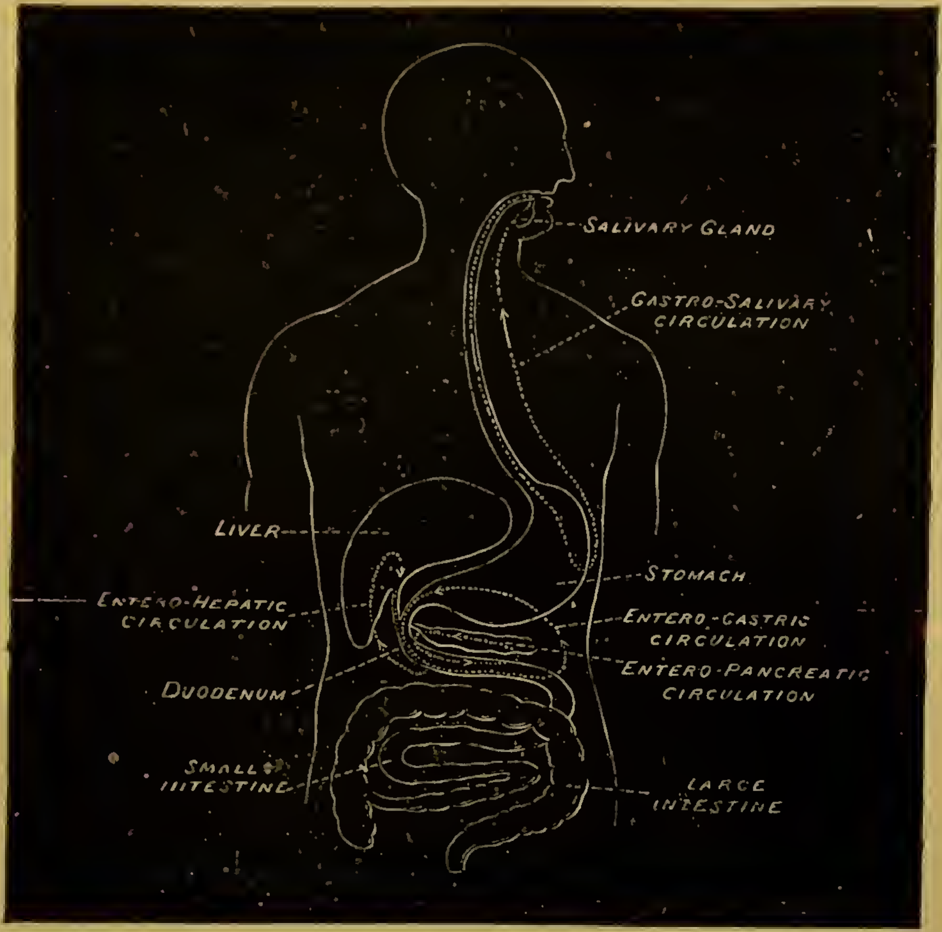

FIG. 126.—Diagram of the gastro-salivary circulation.

Uses.— Saliva is useful in keeping the mouth moist, and thus facilitating mastication, solution, deglutition, and the movement of the tongue in speaking. By moistening the fauces, it also prevents or lessens thirst. A pebble placed under the tongue, or masticated, will keep up a slight flow of saliva, and may be useful for these purposes. Where this is insufficient, dilute acids are employed. As the flow of blood to the glands is greatly increased through secretion, sialagogues have been used as derivatives to lessen inflammation, congestion, and pain, in other parts of the head, as in toothache, earache, and inflammation of the ear, nose, or scalp.

Saliva has also a digestive action on starch, and increase of the flow may be advantageous in imperfect digestion of this substance. When swallowed, the saliva stimulates the secretion of gastric juice, and increased salivary secretion therefore tends to aid the gastric digestion of proteids. To obtain this object it is best to chew a piece of ginger, pellitory, or rhubarb.

Refrigerants.

Refrigerants are remedies which allay thirst, and give a feeling of coolness.

There appear to be two kinds of thirst: one of which is general, the other of which is local. **Local thirst** is occasioned by dryness of the mouth and fauces. It may be quenched by washing the mouth and gargling the throat with water, although none of it be swallowed, or by anything which will increase the flow of saliva, and thus keep the mouth and fauces moist. Thus, a pebble under the tongue, or chewed, will lessen thirst by increasing the secretion of saliva; and acids, both mineral and vegetable, as well as effervescing drinks containing carbonic acid and the juices of fruits, which contain either free vegetable acid or acid salts, acetates and tartrates, have a similar effect. When the secretion from the mouth and throat is very scanty, it is dried up by the passage of air to and fro in the process of respiration. The evaporation thus occasioned may be lessened, and the feeling of thirst diminished by the use of mucilaginous substances, which will form a thin coating over the mucous membrane of the mouth and pharynx. Thus, the addition of oatmeal to water will increase its power to quench thirst, and a very little milk added to water has a similar effect.

General thirst depends upon the condition of the organism generally, which appears to be due either to deficiency of water or excess of soluble and especially saline substances in the circulation.

General thirst is very often accompanied by local thirst, and may be partially alleviated by the means already described, but cannot be removed excepting by the introduction of water into the organism, or removal from it of the saline or other substances which are present in excess, or by lessening the excitability of that part of the nervous system by which the sensation of thirst is perceived.

This part of the nervous system, or thirst centre as Nothnagel calls it, is probably situated, according to him, in the occipital lobes of the brain, and it is possible that it may be irritated directly by mechanical injury, or by the condition of the blood circulating in it, as well as reflexly from mucous membranes, such as that of the mouth and throat, and possibly also from the kidneys. Its excitability is lessened by opium, and this may be used to diminish thirst in cases where other remedies fail to relieve.

Anti-sialics.

Anti-sialics are substances which **lessen** the **salivary secretion.** They may do this:

First, by removing the stimulus to secretion.

Second, by lessening the excitability of the efferent nerves or reflex centres.

Third, by paralysing the efferent nerves, such as the chorda tympani.

Fourth, by acting on the circulation through the gland.

Fifth, by acting on the gland-structures themselves.

Borax and chlorate of potassium are useful in the first of these ways by inducing a healthy condition of the mucous membrane of the mouth, and thus lessening the irritation which gives rise to salivation; opium and morphine diminish the reflex excitability of the nerve-centre, and are thus powerful anti-sialics.

Physostigma in large doses greatly lessens the supply of blood to the gland, and thus diminishes its secretion, and quinine, hydrochloric acid, and alkalies injected directly into the duct of the gland arrest secretion by affecting the secretory cells themselves. These latter drugs, however, cannot be used as anti-sialics.

The most powerful of all anti-sialics is, however, atropine, which paralyses the peripheral terminations of secreting nerves. It does not affect the vaso-dilating nerves, so that in an animal poisoned by atropine electrical stimulation of the chorda tympani will cause dilatation of the vessels and a free flow of blood through the gland as usual, but not a drop of saliva will be secreted. That this absence of secretion is due to paralysis of secretory nerves and not of the secreting cells appears to be shown by the fact that at the time when the power of the chorda to induce secretion is completely paralysed, stimulation of the sympathetic will still induce secretion.

Very large doses of atropine, however, paralyse the secreting power of the sympathetic in the cat, although this has not been noticed in the dog.

The paralysing action of atropine can be counteracted by physostigmine. This is shown by poisoning an animal with atropine, and then injecting physostigmine into the gland of one side through the submental artery. It is then found that irritation of the chorda causes salivation in the gland which has received physostigmine, while it causes no secretion in the other.

Iodide of ethyl-strychnine and cicutine have an action like that of atropine on the secreting and not on the vaso-dilating fibres of the chorda tympani.[1]

ACTION OF DRUGS ON THE STOMACH.

Gastric Tonics.

These are substances which increase the appetite and aid gastric digestion.

From observations made on the stomach in persons or animals

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[1] Jolyet, *Gaz. Méd. de Paris*, 1877

where a gastric fistula has been present, it has been found that in the normal condition, when the stomach is empty and quiet, the mucous membrane is of a pale rose colour. When stimulated mechanically, by rubbing it gently with a feather or glass rod, the mucous membrane becomes redder, and such abundant secretion of gastric juice occurs that it runs down in drops along the walls of the stomach.

When the irritation is greater—as, for example, when the mucous membrane is rubbed roughly instead of gently—an opposite effect is produced. The vessels then contract, the mucous membrane becomes pale, and the secretion of gastric juice stops, secretion of mucus commences, and if the irritation be carried still further, vomiting occurs.

Almost all substances which, when applied to the skin, act as irritants, as arsenic and salts of copper, silver, or zinc, and those also which, without irritating the skin, irritate the nerves of taste,

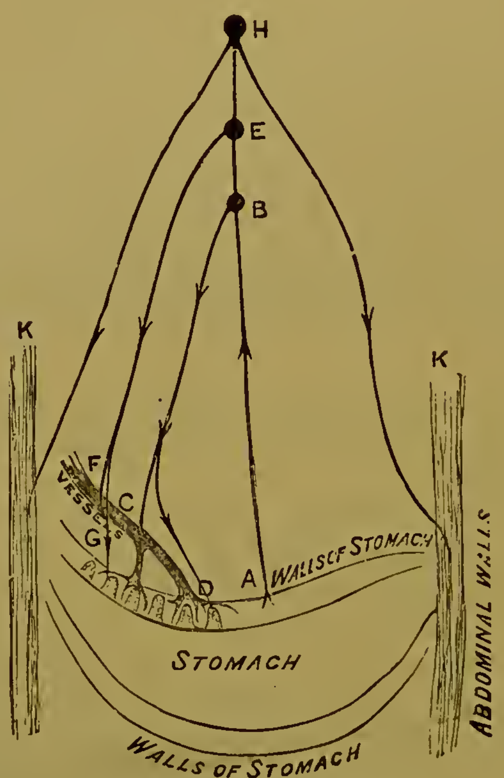

FIG. 127.—Diagram to illustrate the supposed nervous connections of the stomach. A gentle stimulus applied to the walls of the stomach is transmitted by the afferent nerves, A, to a nerve-centre, B, and thence along the vaso-dilating nerves, C, and the secreting nerves, D, to the vessels of the mucous membrane and the cells of the gastric follicles. A stronger stimulus is transmitted up to the nerve-centre, E, and thence along the vaso-constricting fibres. F, and the secreting fibres, G, of the mucous follicles. A still stronger stimulus is transmitted to H, and thence along the motor nerves to the abdominal walls, K K, causing them to contract and produce retching or vomiting.

as bitters, produce a feeling of appetite in the stomach, but they only do this in certain conditions of the stomach, and in certain quantities. The appetite appears to be associated with gentle stimulation of the gastric walls; stronger stimulation destroys

the appetite, still greater irritation causes nausea and, lastly, vomiting.

In cases of atonic dyspepsia, where the stomach is below par, as, for instance, in anæmia and debility, slight stimulants or irritants produce appetite.

In such cases, where the tongue is usually smooth and flabby, bitters and metallic salts are useful. But when the stomach is already too irritable, and the tongue is red with enlarged papillæ, such substances are likely to irritate still more, and thus, instead of increasing the appetite, to diminish it, and produce nausea. The increased irritability of the stomach which precedes a bilious attack is often signalised by an unusually good appetite, which continues during the meal, so that food is eaten with relish. A still greater irritability is characterised by a great appetite before meals, which disappears, giving place to anorexia as soon as a few mouthfuls have been swallowed, and the gastric irritation heightened by the increased circulation consequent on the introduction of the food. In such cases, bitters are likely to do harm, and gastric sedatives, such as bismuth, are required.

The stomach has not merely to receive food, it has to digest it, and in the process of digestion there are **three factors**: 1st, **secretion** of the gastric juice which is to render the food capable of absorption and of assimilation; 2ndly, **movements** of the stomach to break up the food and mix it thoroughly with the solvent juice; and 3rdly, **absorption** of the products of digestion.

Action of Drugs on Secretion in the Stomach.

The **secretion** of the gastric juice is stimulated by gentle mechanical and chemical irritation, as by dilute alkalies and alcohol.

The name of peptogens is given to substances which increase the gastric secretions. Schiff has examined these, and states the most important of them to be dextrine (toasted bread), soups, peptones, &c.[1]

In order to obtain gentle mechanical stimulation, it is often advisable to make patients who are suffering from atonic dyspepsia commence their meals, and especially their breakfast, with solids, instead of commencing with a large draught of liquid.

Dilute alkalies given before meals increase the secretion of gastric juice; so much so, that the alkali is not only rapidly neutralised, but a large amount of acid gastric juice remains over.

The alkaline saliva has a powerful stimulant action on the

[1] Roberts, *Digestive Ferments.*

secretion of gastric juice, and as its quantity is much increased both by savoury food and by the movements of mastication, it is important that the food should not only be well cooked, but slowly and perfectly masticated. Alcohol is one of the most powerful stimulants that we know, and is probably surpassed only by ether. In persons suffering from weak digestion, therefore, a little dilute alcohol with meals is sometimes very beneficial.

Thorough **mastication** is also of the greatest importance in ensuring perfect digestion, inasmuch as the gastric juice penetrates with difficulty, and only slowly dissolves the masses of albuminous matter, while it would digest them very quickly if they were thoroughly broken up.

In children and young people, the stomach may be able to do more than its fair share of work, but it cannot do this in persons above middle age, and in them, imperfect mastication, either from deficient or decayed teeth, or from the habit of eating quickly, is one of the most common causes of dyspepsia.

When the stomach is too much debilitated to secrete a sufficiency of gastric juice, even when stimulated, as in the weakness consequent upon acute disease, general debility, or old age, we may supply **artificially** the **digestive substances** in the form of acids and of pepsin. Acids should be given for this purpose immediately after meals, or two hours after meals. Pepsin should be given either with, or immediately after, those meals which contain albuminous substances. As pepsin has no action on farinaceous food or salts, it is of no use to give it after meals containing these only.

Pancreatin, given two hours after meals, along with a little bicarbonate of sodium, appears, in some cases, to complete digestion, and to give great relief and comfort. When given before meals it is not of much service, since it is rendered inactive by the gastric juice.

Action of Bitters.—There can be no doubt whatever that infusions of vegetable bitter substances are exceedingly useful in dyspepsia. They not only increase the appetite so that more food is taken by the patient, but they really appear to assist digestion and prevent discomfort and flatulence. Their beneficial action is usually supposed to be due to their causing an increased secretion of digestive juices and having an antiseptic action on the contents of the stomach and intestine, thus preventing decomposition and flatulence. This explanation has recently been contradicted, and experiments with a number of bitter substances appear to show that they tend rather to assist than to prevent fermentation and putrefaction, and to lessen the digestive power of the gastric and pancreatic juices. When given in small quantities to animals they cause a slight increase of the gastric juice. They have no action on the secretion of the pancreas; some of them increase slightly the secretion of bile, but not more than could be accounted

for by the water in which they are dissolved. Extract of absinthe appears to increase tissue-change, so that more nitrogen is excreted both in the urine and fæces, while extract of quassia lessens tissue-change by diminishing the amount of food absorbed from the intestine. These experiments would appear to show that bitters instead of being useful are injurious, but the evidence of clinical experience in regard to their utility is so strong that it is evident either that the experiments have been imperfectly conducted, or that we must look to some other organ than the stomach for an explanation of the beneficial action of bitters in dyspepsia. I have just mentioned that the condition of the liver is one of the most important factors in digestion, and this organ appears to be specially acted upon by a number of bodies belonging to the aromatic series (p. 403). As a great number of the vegetable bitters belong to this series, it is possible that their beneficial action in dyspepsia may be due to changes which they induce in the liver (p. 368) rather than in the stomach.

Action of Drugs on the Movements of the Stomach.

Digestion is greatly aided by the **movements** of the stomach, which assist it by breaking up the food and mixing it thoroughly with the gastric juice. When these are deficient, it is probable that they are stimulated by nux vomica, or strychnine, and also by bitters.

A number of experiments have lately been made by Schütz[1] on the influence of drugs upon the movements of the stomach. These experiments are interesting as showing an analogy between the action of drugs on the stomach and other organs, such as the heart; but the doses applied were so large that the effects are not to be considered the same as those arising from medicinal doses. These experiments were made by observing the movements of the viscus, after removing it from the body and placing it in a moist chamber. Various drugs were administered to dogs; and after the symptoms of poisoning became well-marked, the animals were killed, and the movements of their stomachs in the moist chamber were compared with those of normal animals.

The movements of the isolated stomach depend upon:

(*a*) The muscular fibres contained in its walls.

(*b*) The motor nerve-endings by which the muscular fibres are excited to action.

(*c*) The ganglionic cells of Auerbach's plexus, by which the rhythmical movements of the organ are maintained.

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[1] *Arch. f. exp. Path. u. Pharm.*, xxi., p. 341.

(*d*) The sensory nerves, by which those ganglia may be reflexly excited.

The occurrence of spontaneous movements in the stomach shows that both the ganglia and muscular fibres retain their functional power. This is shown also by the occurrence of reflex contractions, when the stomach is distended by inflation and by the production of extensive undulating contractions on local irritation by a weak electrical stimulus. As the stomach dies, the nervous apparatus loses its irritability before the muscles, so that spontaneous movements cease, reflex contraction no longer occurs on inflation, and the strength of electrical stimuli requires to be greatly increased in order to produce undulatory movements extending beyond the part actually stimulated.

When the excitability of the nervous apparatus is quite gone, that of the muscular fibres still remains. Electrical stimuli cause localised contractions corresponding to the bundles of muscular fibres directly excited by the current.

It is evident that this result will be nearly the same if the ganglia themselves are paralysed, or if the motor nerve-fibres, through which they act on the muscular fibres, are paralysed. At present, these actions have not been distinguished experimentally in the stomach, and therefore conclusions regarding the mode of action of some drugs are based to some extent upon analogy. Thus, ether and atropine both produce the effect mentioned above; but we know that ether tends to act on nerve-centres, such as those of the brain and spinal cord, while atropine tends to paralyse peripheral nerves ending in involuntary muscular fibre. The conclusion is that in the stomach also the effects of ether are due to its action on the ganglionic cells, while those of atropine are due to its action on motor nerves.

When the muscular fibres are paralysed as well as the nerves, electrical stimuli cause no contractions at all, or local contractions, which are more or less feeble according to the completeness of the paralysis.

The results of Schütz's experiments are as follows :—

Muscular irritability is increased, so that finally general persistent contraction of the stomach occurs, by :—

Physostigmine.	Scillain.
Digitalin.	Helleborein.

Motor nerve-endings in the stomach are

Excited by	Paralysed by
Muscarine.	Atropine.

The excitation by muscarine is shown by general contraction of the stomach. The symptoms of paralysis by atropine have been already discussed.

Automatic nerve-centres in the stomach are **excited**, so that the spontaneous movements become brisker and assume a character differing from the normal—

Strongly by—	Less marked by—
Emetine.	Strychnine.
Tartar emetic.	Caffeine.
Apomorphine.	Veratrine.
	Barium chloride.
	Nicotine } in small doses.
	Pilocarpine } in small doses.
	Cocaine (?)[1]

Automatic nerve-centres are partially **paralysed**, so that the movements are weakened, though not completely abolished, by—

Chloral.	Arsenic.
Urethane.	Nicotine } in large doses.
Morphine.	Pilocarpine } in large doses.
Pyrophosphate of zinc.	

The whole nervous mechanism of the stomach is paralysed by exposure to the vapour of

Chloroform. Ether.

This paralysis is transient, and only lasts during exposure. The administration of chloroform or ether to animals so as to produce ordinary anæsthesia seems to have no action on the movements of the stomach. It must be borne in mind that while exposure to the vapour of ether or chloroform may paralyse the stomach, and that while this action is unimportant, as it may occur from an overdose of these substances, smaller doses probably increase the movements of the stomach and act as carminatives.

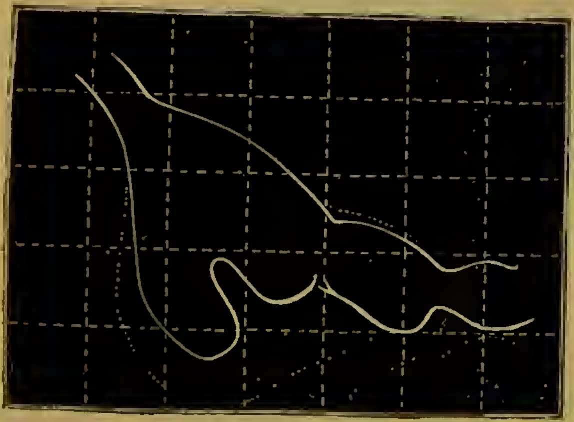

FIG. 128.—Action of tartar emetic on the stomach in producing active contraction of an antiperistaltic character. The dotted line shows the shape of the stomach at rest.

[1] Cocaine at first causes greatly increased movement of the stomach, but its subsequent efforts are similar to those of atropine.

Absorption from the Stomach.

We know at present very little regarding the effect of drugs in stimulating **absorption** from the stomach, but it is probable that this is very greatly influenced by the condition of other organs.

All the processes which go on in the stomach—secretion, peristaltic action and absorption—are much influenced by the condition of the circulation.

All the blood which circulates in the stomach has to pass through the liver before it gets into the general circulation

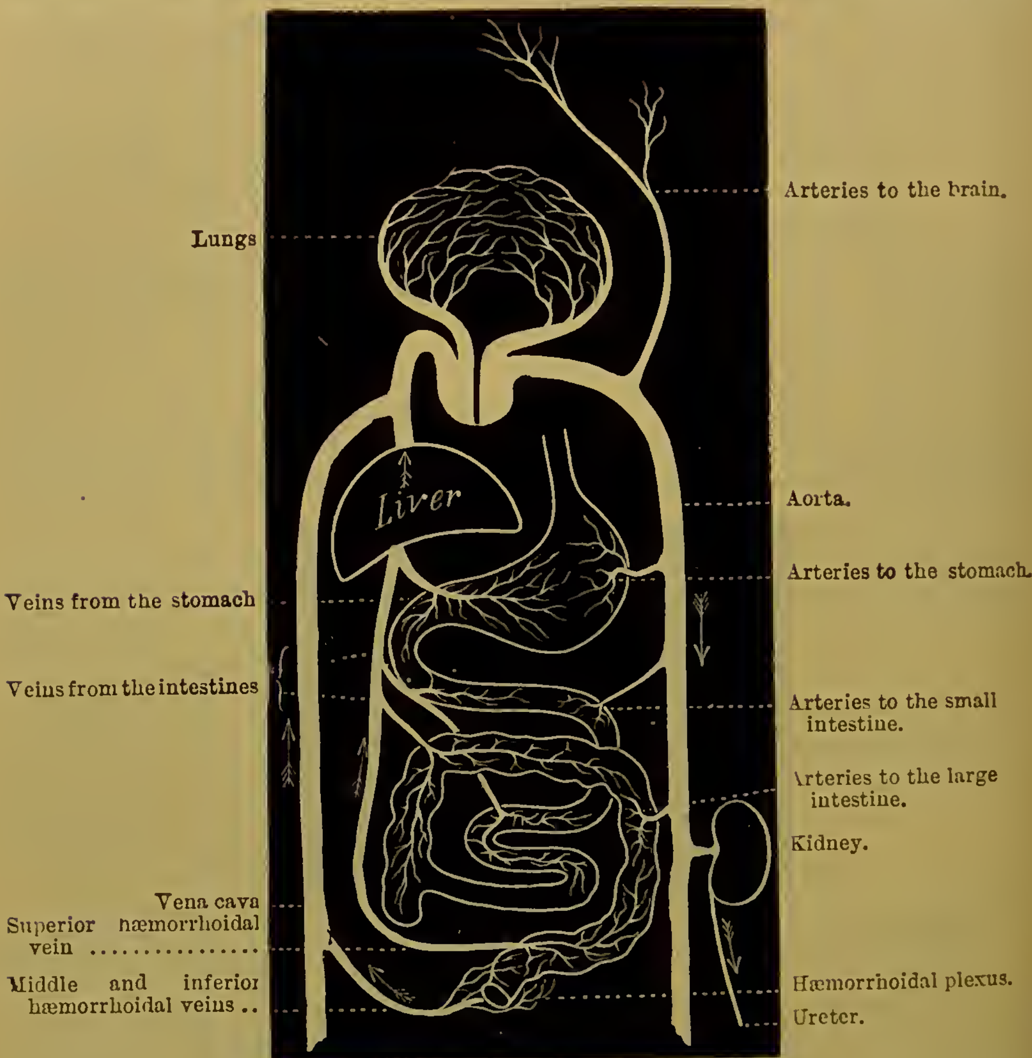

FIG. 129.—Diagram of the veins forming part of the portal circulation. The pancreatic and splenic veins, although most important, have been omitted for the sake of clearness.

(Fig. 129), and thus the condition of the stomach is necessarily much modified by the condition of the liver. If there is any obstruction to the free flow of blood through the liver, the circulation in the stomach will necessarily be impeded, and absorption probably diminished.

Not only the blood from the stomach, but that from the intestines also, passes through the liver, and we may naturally expect that the liver itself will be influenced by the condition of the blood which passes to it from the intestinal canal.

In Dr. Beaumont's observations on Alexis St. Martin, in whom a gastric fistula existed, he found that after the stomach had been deranged by various articles of food, including fat pork, there was distress in the stomach, headache, costiveness, and a coated tongue. In the stomach there were numerous white and pustular-looking spots. Half a dozen calomel pills produced catharsis, removed the symptoms, and restored the mucous membrane of the stomach to its normal condition. Whether this effect was due to the action of the pills on the liver, or on the intestines, we cannot perhaps positively say, but at all events the improvement was readily evident to the observer's eye.

Purgatives and **Cholagogues** may thus act as **indirect gastric tonics**,[1] and the effect of bitters (p. 364) may be due to their action on the liver.

Absorption from the stomach is probably also much influenced by the condition of the nervous system. Bouley found that when the vagi were divided in a horse, strychnine no longer produced poisoning, the reason being that the absorption took place so slowly after a division of the nerves that the poison was excreted as fast as it was absorbed. The retarded absorption, however, he considers to be due, not to any alteration in the absorptive power of the stomach itself, but to diminished movement in its walls, so that its contents are not so quickly poured out into the intestine. Absorption normally goes on more slowly from the stomach than from the intestine, and so while the poison remains in the stomach it is not absorbed quickly enough to cause poisoning.

Antacids.

Antacids are remedies employed to lessen or counteract acidity. The excessive acidity for which antacids are given may be present in the stomach, intestines, or urine.

Antacids are divided into **direct** and **indirect** or remote. Direct antacids lessen the acidity in the stomach, to which they are directly applied. Remote antacids lessen the acidity of the urine. Some substances have both actions, such as potash and soda, or the carbonates and bi-carbonates. Other substances, such as the citrates, tartrates, and acetates of these bases, have no power to lessen acidity in the stomach, but, after absorption into the blood, they appear to undergo combustion, and become converted into carbonates. In this form they are excreted in the urine, and lessen its acidity.

[1] Beaumont, *Physiology of Digestion*, Burlington, 1847, p. 118.

Ammonia and its carbonate are direct antacids, but not remote antacids. They lessen acidity in the stomach or intestines, but after absorption they undergo change, and are eliminated in the form of urea, and, according to some, of nitric acid, so that they do not lessen the acidity of the urine.

Direct Antacids.—Liquor potassæ, potassium carbonate, potassium bi-carbonate, liquor sodæ, sodium carbonate, sodium bi-carbonate, liquor lithiæ, lithium carbonate, lithium bi-carbonate, magnesia, magnesium carbonate, magnesium bi-carbonate, lime-water, saccharine solution of lime, chalk.

Direct but not Remote Antacids.—Ammonium carbonate, aromatic spirit of ammonia.

Remote Antacids.—Potassium acetate, potassium citrate, potassium tartrate, potassium bi-tartrate, sodium acetate, sodium citrate, tartarated soda, lithium citrate.

Emetics.

These are remedies which **produce vomiting.**

Action.—The act of vomiting consists in compression of the stomach by the simultaneous spasmodic contraction of the diaphragm and abdominal muscles, while at the same time relaxation of its cardiac orifice is produced by contraction of the fibres which radiate out from the lower end of the œsophagus along the gastric walls. By their contraction these fibres draw the stomach up towards the diaphragm and pull the walls of the œsophagus apart at its lower end so as to open the cardia. When the cardiac orifice dilates at the same moment that the stomach is compressed between the diaphragm and the abdominal muscles, its contents are expelled and **vomiting** occurs; but when the compression of the stomach and dilatation of the cardiac orifice do not take place simultaneously, the contents of the stomach are retained and the efforts are then termed **retching.**

The **nerve-centre** which regulates the movements of vomiting is situated in the medulla oblongata. The movements of vomiting are modified respiratory actions, and the respiratory centre appears to be closely connected with the vomiting centre. Indeed some groups of ganglion cells probably take part both in respiration and vomiting, or in other words form part of both the respiratory and vomiting centres (Fig. 80, p. 235).

The reason for this supposition is not merely that the movements of vomiting consist of modified respiratory movements, but that drugs which cause vomiting also increase the respiratory activity. Emetics usually quicken the respiration considerably before they produce vomiting, and if injected into the veins they not only quicken the respiration, but prevent the condition of apnœa being produced by vigorous artificial respiration.

On the other hand, the desire to vomit may be lessened to

some extent by taking frequent and deep inspirations, and narcotics which diminish the excitability of the respiratory centre also lessen the tendency to vomit.

The **motor** impulses from the vomiting centre are sent to the abdominal muscles, diaphragm, stomach and œsophagus by the intercostal, phrenic, and vagus nerves respectively. Section of the vagi generally, though not always, destroys the power to vomit, because it disturbs the co-ordination of the cardia and the abdominal muscles and diaphragm, so that they no longer act simultaneously, and vomiting does not occur, although retching may continue.

The vomiting centre is usually excited by stimulation of **afferent** nerves passing upwards to it from the body, or by impulses sent down to it from the brain.

The **brain** may be stimulated so as to act on the vomiting centre in the medulla through impressions on the nerves of special sense, such as a disgusting sight, stench, or taste, or by the recollection of such subjects. Irritation of the brain itself or of its membranes by inflammation, tubercle, hæmorrhage, softening, or cancer may also excite vomiting. The **afferent nerves** are shown in the accompanying diagram (Fig. 130). Those chiefly concerned with the action of emetics are:—

1. Branches of the glosso-pharyngeal nerve to the soft palate, the root of the tongue, and the pharynx. Tickling these parts with the finger or with a feather is one of the readiest means of inducing vomiting. Vomiting also occurs when the soft palate, tonsils, or pharynx are inflamed, especially in children.
2. The nerves of the stomach. These are chiefly branches of the pneumogastric, but they are contained also in the sympathetic system.
3. Mesenteric nerves causing vomiting in hernia.
4. Nerves of the liver and gall-duct.
5. Nerves of the kidney and ureter.
6. Vesical nerves.
7. Uterine nerves.
8. Pulmonary branches of the vagus causing vomiting in phthisis.

There are also a number of other nerves which produce vomiting, but are more important in connection with pathological vomiting than with the action of emetics.

When less was known regarding the action of the nervous system in vomiting, **Emetics** were divided, according to their relation to the stomach, into direct and indirect. **Direct** emetics were those which acted only when introduced into the stomach. **Indirect** were those which acted when injected into the blood.

Their relation to the vomiting centre is of course the reverse. Drugs which are applied directly to the stomach act reflexly or indirectly on the vomiting centre, while those injected into the

blood may be carried by the circulation to the medulla and act directly upon it.

It is to be noted, however, that drugs injected into the circulation are carried not only to the nerve-centres but to the stomach,

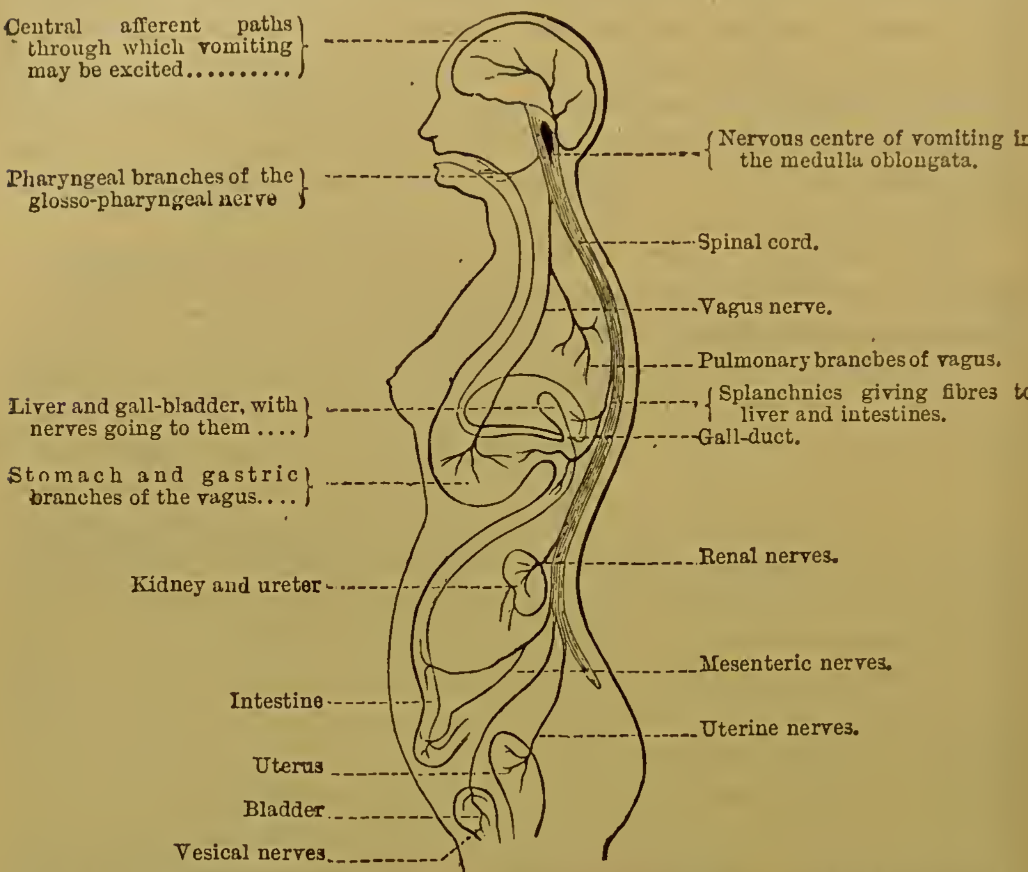

FIG. 130.—Diagram showing the afferent nerves by which the vomiting centre may be excited to action.

and may be excreted by the gastric mucous membrane. They may thus irritate the afferent nerves of the stomach and stimulate the vomiting centre reflexly just as they do when given by the mouth. Thus it has been shown by Brinton that tartar emetic injected into the veins of a dog is excreted in a few minutes into the stomach, and may be found on testing its contents.

It is therefore evident that the action of drugs in causing vomiting may be complex, and that drugs injected into the blood or under the skin may cause vomiting, both by (1) irritating the vomiting centre in the medulla directly when conveyed to it by the circulation; and (2) by irritating it reflexly from the stomach, whither they have also been conveyed by the blood.

It is frequently very difficult to determine in which of these two ways a drug has acted, and sometimes almost impossible to decide with certainty.

The reasons for believing that any drug injected into the circulation has caused vomiting by irritating the medulla reflexly through the stomach, and not by acting directly upon it, are:

(*a*) When the vomiting does not take place immediately on injection, but only after sufficient time has elapsed to allow of excretion of the drug into the stomach.

(*b*) When the quantity of a drug required to produce vomiting by injection into the veins is greater than that which is sufficient to produce a similar effect if introduced into the stomach. It is probable that some drugs, as tartar emetic, act in both ways, because, as has already been mentioned, it is excreted into the stomach and will there act as an irritant.

But it will also produce vomiting when the stomach has been excised and replaced by a bladder, as in Magendie's celebrated experiment. Even this experiment, however, does not prove that tartar emetic acts directly on the vomiting centre, inasmuch as it is possible that it may be excreted by the œsophagus or intestines and irritate the vomiting centre reflexly through them. As tartar emetic, however, appears to act as an irritant chiefly in those parts of the body where there is an acid secretion, it seems doubtful whether it would produce irritation in the œsophagus and intestines such as it does in the stomach. It therefore seems not improbable that the vomiting which it occasions after excision of the stomach is due to its direct action on the medulla oblongata, but this cannot be regarded as quite proved. In order to avoid the confusion which the terms **direct** and **indirect** emetics are likely to produce with regard to their relations to the stomach and vomiting, it is better to describe them as, and to employ the terms, **topical** or **local** and **general** emetics.

Topical, or local, are such as produce vomiting by acting locally on the pharynx, œsophagus, or stomach; and **general**, such as act through the medium of the circulation. The line between the two is not distinct, inasmuch as tartar emetic will produce vomiting in either way, and so will sulphate of zinc, or sulphate of copper. The *local* action of sulphate of zinc and sulphate of copper, however, on the stomach is so much greater than their general action that they may be classed among the *local* emetics.

Local Emetics.

Alum.
Ammonium carbonate.
Copper sulphate.
Mustard.
Salt.
Subsulphate of Mercury.
Water (lukewarm and in copious draughts).
Zinc sulphate.
Strong infusions of vegetable bitters, as camomile, quassia, &c.

General Emetics.

Tartar emetic.
Ipecacuanha and Emetine.
Apomorphine.
Senega.
Squill.
Muscarine, Urechitine, Digitalis and its congeners, } not used medicinally as emetics.

The action of **local** emetics is confined to that of producing vomiting, which is generally not long continued, ceasing after the emetic has been evacuated, and is not accompanied by much general depression.

The vomiting occasioned by **general** emetics, on the other hand, is much longer continued, and is accompanied by great general depression, nausea, languor, muscular weakness, enfeeblement of the circulation, and increase of the secretions, especially those of saliva, sweat, and mucus in the œsophagus, stomach, and bronchial tubes.

Uses.—Emetics may be used for the purpose of simply **emptying the stomach**, or the violent expulsive efforts which they occasion may be utilised in order to remove foreign bodies or secretions from the œsophagus or from the biliary or respiratory passages.

1. Emetics may be used to cause the **expulsion of foreign bodies**, such as pieces of gristle or meat which have become impacted in the upper part of the œsophagus, and, by pressing on the larynx, are giving rise to suffocation. In such cases apomorphine given subcutaneously, or injected into a vein in the dose of $\frac{1}{12}$th or $\frac{1}{10}$th of a grain, will be found of service.

2. They may be used to **remove the contents of the stomach** when these, instead of undergoing digestion and absorption in the normal manner, have undergone fermentative changes and become acid, acrid, and irritating, giving rise to pain, either in the stomach itself, or in some other organ, as in the head. In gastralgia, or in headache either depending upon indigestion, or associated, like sick-headache, with a tendency to vomiting, large draughts of warm water often give relief. Their emetic action may be aided if necessary by tickling the fauces with the finger, or by using strong camomile tea, or mustard and water in place of water alone. Simple draughts of warm water, however, may relieve the gastralgia or headache without causing vomiting. They appear to do so by simply diluting the acrid contents of the stomach so much that they no longer irritate the mucous membrane.

3. Emetics **remove the poison** from the stomach in cases where it has been swallowed. Here mustard and water is very useful, as it is the emetic which is most likely to be at hand; but sulphate of copper and sulphate of zinc if readily procured are to be preferred, as they empty the stomach most quickly and effectually. In cases of poisoning by laudanum, the nerve-centres are so much deadened by the narcotic that they may not respond to the stimulus even of large doses of these emetics, and then it may be necessary to employ the stomach-pump or gastric syphon.

4. To **expel bile** from the gall-bladder, to drive small **gall-stones** through the gall-duct. The bile is secreted under a very

low pressure, and a very slight obstruction in front may prevent its flow through the gall-duct and occasion its accumulation in the gall-bladder and biliary capillaries. The compression of the liver between the diaphragm and abdomen muscles, even in ordinary respiration, tends greatly to dispel the bile from the liver, and this expulsive action is of course greatly increased during the violent efforts of vomiting. During these efforts the bile may be forced through the gall-duct, driving before it the obstruction which has been occasioned by the accumulation of mucus within it due to catarrh, or by the impaction of a small biliary calculus. In this manner emetics may remove jaundice due to obstruction.

5. To **remove bile** from the body in cases of **biliousness, fevers,** and **ague.** In biliousness the emetics have got the double action of expelling the bile from the liver in the way just mentioned, and of removing it from the body through the stomach. When bile passes along the intestines, not only is it re-absorbed, but poisonous matters from the intestine are absorbed with it. When it is ejected from the stomach by the efforts of vomiting, no time is allowed for its re-absorption, and so both the bile itself, and any poisonous matter which it contains, are more rapidly and certainly removed from the body. It is probable that the malarious poison circulates in the bile, and possibly also other poisons which give rise to fevers. There can be no doubt of the advantages to be derived from the use of emetics in ague before the administration of quinine; and indeed cases of ague may be sometimes cured by the use of emetics alone without quinine, while quinine without emetics is not unfrequently of very little use in bad cases. Emetics have also been recommended in the early stages of continued fevers, in order to remove the poison on which they are supposed to depend. For such purposes ipecacuanha or tartar emetic is best.

6. To **remove obstructions** from the **air-passages,** such as false membranes from the trachea and bronchia in croup or diphtheria, or the over-abundant secretion which is clogging the bronchi and interfering with respiration in bronchitis, and more rarely in phthisis. Ipecacuanha is the emetic most readily chosen in such cases, as it tends to increase the secretion from the air-passages, as well as to produce vomiting. When it does not act rapidly, sulphate of zinc or sulphate of copper may be used, and a teaspoonful of alum is a very efficient remedy in croup. When there is much depression of the circulation, carbonate of ammonium is to be preferred as an emetic, inasmuch as it stimulates the circulation, as well as causes vomiting.

Contra-indications.—Emetics must be avoided in persons suffering from **aneurism,** and used with care in persons suffering from **atheroma** or a tendency to **hæmorrhage** from the lungs or uterus, lest the high blood-pressure which occurs during the

efforts of vomiting should lead to the rupture of a blood-vessel. They should be used with caution also in persons suffering from **hernia**, or who have a tendency to it, or from **prolapsus** of the uterus. In pregnancy we often find obstinate vomiting lasting for a length of time, and yet producing no abortion; but where a tendency to **abortion** exists, emetics should be avoided if possible.

Anti-emetics and Gastric Sedatives.

Gastric sedatives are substances which lessen the irritability of the stomach and thus diminish pain, nausea, and vomiting.

Their action may be either **local** on the stomach, or **general** on the nervous system, and especially on the vomiting centre in the medulla oblongata.

Local Sedatives.

Alcohol.
Alum.
Arsenious acid in minute doses.
Atropine.
Belladonna.
Bismuth salts.
Carbolic acid.
Cerium oxalate.
Chloroform.
Cocaine.
Creasote.
Ether.
Hydrocyanic acid.
Ice.
Morphine.
Opium.
Resorcin.
Silver nitrate.
Sulpho-carbolates.

General Sedatives.

Hydrocyanic acid.
Morphine.
Opium.

Anti-emetic Measures.

Recumbent posture.
Injection of large quantities of aërated water into the rectum.

The most powerful of all **local** sedatives is ice, and when vomiting is persistent, everything should be iced, and ice swallowed in small lumps. Hydrocyanic acid and morphine probably act by lessening the irritability of both the nerves in the stomach itself and of the vomiting centre as well. The mode of action of creasote and carbolic acid is rather uncertain, because, although they have a local anæsthetic action, yet they are found useful also in cases of reflex vomiting, such as the vomiting of pregnancy.

As **adjuvants** to gastric sedatives, we may mention such substances as diminish or remove the irritation, although not

lessening the sensibility, of the stomach itself. Thus, where the irritant consists of very acrid fluid in the stomach, a large draught of water, by diluting it, may lessen pain, or nausea, and alkalies have a similar action. When the irritation is due to congestion of the mucous membrane, **astringents** will also have a sedative action. Probably this is the explanation of the use of alum in the vomiting of phthisis, and possibly, also, of the use of nitrate of silver in the vomiting of chronic alcoholism.

Uses.—Gastric sedatives are employed (1) to **relieve pain** in the stomach, as in gastrodynia. The most useful are small doses of morphine, hydrocyanic acid, belladonna, arsenic, and bismuth; (2) to **relieve vomiting**. This depends upon the cause of the vomiting. When it is due to acrid substances in the stomach, the best sedative is often a large draught of warm water, which either dilutes or renders them less irritating, or causes their removal by vomiting.

Where it is due to acute irritation of the walls of the stomach itself, ice, hydrocyanic acid and morphine, and bismuth are best.

When due to the acrid products of fermentation in the stomach, sulphurous acid, creasote, resorcin, and the sulpho-carbolates are very useful.

When due to chronic irritation and congestion, alum, nitrate of silver, creasote, carbolic acid, and the sulpho-carbolates are serviceable.

When the vomiting is due to strangulated hernia, the hernia must be reduced, and in cases of intussusception or obstruction these conditions must be removed. In the vomiting of pregnancy, the irritability of the vomiting centre must be reduced by bromide of potassium or morphine. It is only in extreme cases that the source of irritation, viz. the pregnant condition, is to be removed, but certain local means are sometimes useful; such are separation of the membranes around the neck of the uterus, which may possibly act by lessening the irritation in the organ, and painting the os uteri with stimulating applications which probably rather act by a kind of counter-irritation or inhibition.

The vomiting of pregnancy has sometimes been arrested by the injection of effervescing water, and especially of natural effervescing chalybeate water like that of Pyrmont, into the rectum in quantities of two litres at a time. It is difficult to say whether this is due to a local or general sedative action of the carbonic acid or to reflex inhibition of vomiting (cf. inhibition of sneezing, p. 246).[1]

[1] Schücking, *Deutsch. Med. Ztg.*, ii. 1885.

Carminatives.

Carminatives are substances which aid the expulsion of gas from the stomach and intestines. They appear to do this by increasing the peristaltic movements of these organs, and in the case of the stomach by causing the lower end of the œsophagus or cardiac sphincter, and perhaps sometimes the pyloric sphincter, to dilate so as to allow of the exit of gas. The stomach naturally contains a certain amount of gas, chiefly nitrogen and carbonic acid. The nitrogen is derived from air which has been swallowed, the oxygen with which it was mixed being absorbed by the walls of the stomach.

For respiration goes on in the stomach, as well as in the lungs, though only to a slight extent in mammals, and oxygen is absorbed and carbonic acid excreted. The stomach, therefore, generally contains carbonic acid in addition to nitrogen; some of the carbonic acid also is derived from the food. In addition to these gases there is frequently hydrogen present: hydrogen and a quantity of carbonic acid being formed by processes of fermentation going on in the food. Sometimes instead of pure hydrogen marsh-gas is formed, which takes fire when expelled from the stomach, and not unfrequently the hydrogen unites with sulphur, forming sulphuretted hydrogen, causing to the patient an unpleasant taste of rotten eggs in the mouth, or giving their smell to the breath. It is probable that this last occurrence is due in many cases to the presence and decomposition in the stomach of bile, which contains sulphur as one of its constituents.

When digestion is rapid and complete, little or no fermentation occurs, very much less gas is formed, and therefore there is no uncomfortable distension.

There are several drugs which tend to prevent fermentation, while they hardly interfere at all with the action of the gastric juice. Among these may be mentioned creasote, sulphurous acid, and bitters, though the anti-fermentative action of the last has been denied. These substances may all be regarded as **adjuvants** to carminatives, and so indeed may pepsin, dilute alkalies, and all other remedies which stimulate the secretion of gastric juice and thus aid digestion.

Where there is any tendency to venous congestion in the stomach, there will be interference with the respiration in the stomach, and thus a greater tendency to the accumulation of gas. Any conditions interfering with the circulation, such as mitral disease or hepatic congestion, will thus tend to cause flatulence, and in such cases digitalis and cholagogues will prove useful adjuvants to carminatives.

It is possible that much mucus covering the surface of the stomach may interfere both with absorption and with gastric respiration. Charcoal has been given to remove flatulence, on the

supposition that it absorbs the gases in the stomach. But it only absorbs gas when it is dry, and the beneficial action which it certainly possesses is probably a mechanical one in removing mucus and stimulating circulation. Possibly bismuth, nitrate and carbonate, and magnesium, oxide and carbonate, act similarly, though less powerfully.

The chief **Carminatives** belong to the classes of aromatic oils, alcohols, or ethers. They are:—

Allspice and oil.	Cinnamon and oil.	Mace.
Anise and oil.	Cloves and oil.	Mustard.
Asafœtida.	Coriander and oil.	Nutmeg and oil.
Cajeput oil.	Dill and oil.	Pepper.
Capsicum.	Ether and acetic ether.	Peppermint and oil.
Caraway and oil.	Fennel.	Spearmint and oil.
Cardamoms.	Ginger.	Spirits.
Chilies.	Horseradish.	Valerian and oil.
Chloroform.		

Uses.—Carminatives are employed (1) to remove pain and distension of stomach and intestines caused by **flatulence**; (2) to render peristaltic action regular, and diminish local **spasm** and pain depending upon it. They are useful both in cases where the spasm is due to irritation of the stomach and intestines by irritant articles of food, irritant secretions, or irritant medicines. They are therefore commonly used not only in griping and colic pains due to indigestion, worms, or exposure to cold, but as adjuvants to purgatives in order to lessen the griping pain, which they often cause when given alone. In addition to this, by rendering the peristaltic action of the bowel more regular, they assist the action of the purgatives.

ACTION OF DRUGS ON THE INTESTINES.

Intestinal Movements and Secretion.—The peristaltic movements of the intestine occur even when it is separated entirely from the body. Their rhythmical occurrence appears to be due to the action of the ganglia contained in Auerbach's plexus, which lies between the outer longitudinal and internal circular layer of the muscular coat. The **secretion** is probably influenced by Meissner's plexus, which lies in the sub-mucous coat.

Both the movements and the secretion of the intestine require to be regulated in accordance with the wants of the body, and this is done by the **nerves** which connect these plexuses with the cerebro-spinal centres. The chief of these nerves are the splanchnics and the vagi. Irritation of the vagi frequently causes movements of the intestine; irritation of the splanchnics, on the other hand, arrests them, so that the splanchnics have been regarded as the inhibitory nerves of the intestine, just as the vagi are the inhibitory nerves of the heart. But this arrest is by no means

constant; sometimes the movements instead of being arrested are distinctly increased; so that it is evident that the splanchnics contain a mixture of stimulating and inhibitory fibres, or else that the same fibres are capable of exercising either function under different conditions.

Paralytic Secretion.—When all nervous connection between the intestine and the higher nerve-centres is cut off by completely dividing the intestinal nerves, a copious secretion, exactly resembling the rice-water stools of cholera, occurs in the intestine. This is best shown by isolating three loops of intestine, by means of ligatures, after they have been previously carefully emptied, as shown in Fig. 131. The nerve-fibres going to the middle loop are then divided, and the intestine is returned to the abdominal cavity. After four or five hours the animal is killed, and the intestine examined; it is then found that the loop, the nerves of which have been divided, is filled with fluid, while the other loops which have been under precisely the same circumstances, but the nerves of which have not been cut, remain empty.

It is evident, then, that certain **nerve-centres** possess the power of **restraining** the **secretion** from the intestine. These nerve-centres have been shown by Pye-Smith and myself to be the smaller or inferior ganglia of the solar plexus, with the superior mesenteric off-set from them. When these ganglia are destroyed, the same abundant secretion occurs in the intestine

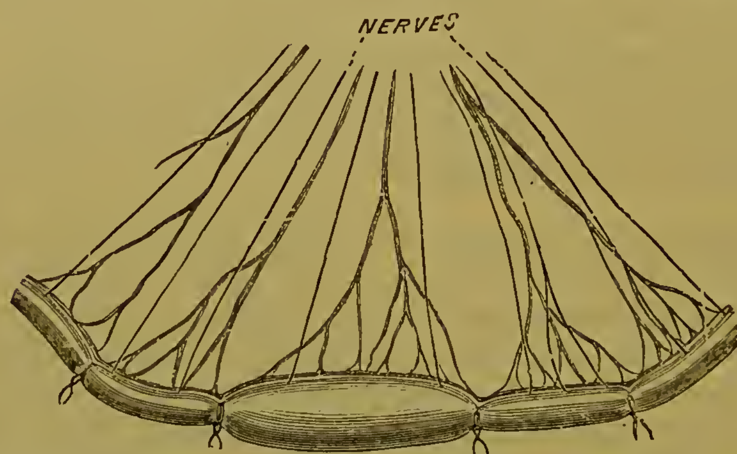

FIG. 131.—Diagram showing the effect of section of nerves on secretion from the intestine. The nerves going to the middle loop have been divided, and it is distended with the fluid secreted.

as when all the nerves are cut, but if these ganglia be left intact the spinal cord may be removed, the vagi and splanchnics cut, and the semilunar ganglia excised without any excessive secretion occurring in the intestine.

The **vascular supply** of the intestines is regulated to a considerable extent by the splanchnics, irritation of which causes contraction of the vessels. There appears also, however, to be an important relation between the intestinal vessels and the lumbar portion of the spinal cord, because when this part of the cord is

destroyed with extirpation of the solar plexus, hæmorrhage or hyperæmia of the intestinal mucous membrane occurs, so that the internal surface of the intestine has a somewhat dysenteric appearance. This does not occur when the solar plexus and semilunar ganglia are destroyed, the splanchnics divided, or the mesenteric nerves cut.[1]

The nervous arrangements for regulating intestinal movement and secretion are evidently exceedingly complex, and until our knowledge of their physiological relations is more perfect, we cannot expect to understand completely the effect which drugs produce upon them. These are occasionally very complicated, and vary considerably according to the quantity of the drug used. **Drugs** may affect the intestine by their **local** action on the intestine itself, by their **direct** action on the **central nervous** system, or by their **indirect** action through the alterations in the quality or supply of the blood. The quality of the blood which circulates in the intestine alters its movements very considerably.

When the aorta is clamped, so that the blood which circulates in the intestine and in the lower part of the spinal cord becomes venous, the peristaltic movements are usually much increased; when the compression is removed and arterial blood is allowed to circulate again, the peristalsis, instead of diminishing, as one might expect, becomes still more intense. Compression of the vena cava inferior, or of the portal vein, sometimes causes a slight increase in the peristaltic movements, but it is inconsiderable as compared with those produced by clamping the aorta. During **suffocation**, when the blood becomes venous throughout the whole body and exercises an irritating action, not only on the nerve-centres present in the intestine and in the lumbar portion of the spinal cord, but also on the brain and upper part of the cord, the effect on the movements of the intestine is variable. They are sometimes increased, but sometimes an inhibitory effect appears to be produced through the higher centres and their movements are arrested.

It is evident therefore that when an animal has been poisoned by any drug, and the intestines are examined after death, two **different conditions** may be found, which do not depend upon any peculiar action of the drug on the intestine, but only upon its effects on the higher nerve-centres; thus, if the higher centres have been in such a condition as to cause inhibition, the intestines may be found in a state of perfect rest, whereas, if they happen not to be in this condition, brisk peristalsis may be observed. It very often occurs that when the intestines are first exposed after an animal's death, they are found to be at rest, but as the higher centres die from a stoppage of the circulation, the peristaltic movements become much accelerated.

[1] T. Lauder Brunton and Pye-Smith on 'Intestinal Secretion and Movement,' *British Association Reports*, 1874, 1875, 1876.

In order to simplify the problem presented by the complicated nervous arrangement in the intestine, Ludwig and Salvioli have used the plan of keeping up the circulation artificially in a small piece of intestine, and then investigating its movements under various conditions. The intestine was laid on a piece of

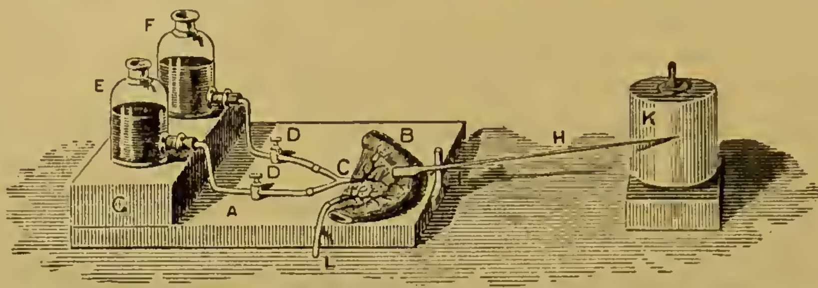

FIG. 132.—Diagrammatic representation of apparatus for testing the action of drugs on the intestine by artificial circulation through it. For the sake of simplicity the means employed to keep up the temperature of the intestine and apparatus have been omitted. A, a board on which the intestine, B, is laid. C, a cannula tied into a branch of the mesenteric artery. D. D, two stop-cocks, by means of which pure blood or poisoned blood may be passed at will through the cannula. E and F, two flasks containing pure and poisoned blood. G, a block on which they stand, and by which they can be raised to a greater or less height, so as to alter the pressure under which the blood flows. When the apparatus is kept warm the pressure is more easily regulated by passing air into the flasks from a pressure bottle. H, the lever for registering the movements of the intestine. One end is weighted and rests on the intestine. I is the axis on which the lever works. K is a revolving cylinder on which the movements are recorded.

FIG. 133.—Shows the effect of anæmia. The upper tracing shows the movements of the intestine supplied with normal blood; the lower shows the movements of an intestine rendered more vigorous by anæmia.

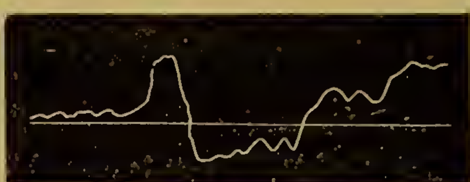

FIG. 134.—Shows the effect of peptones. The first half of the tracing shows the movements of an intestine supplied with blood thoroughly oxygenated; the second half shows the effect of blood containing peptones.

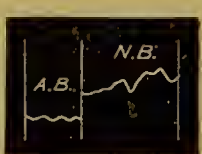

FIG. 135.—Shows the effect of nicotine. The part of the tracing marked *A B* shows the intestinal movements during the circulation of blood saturated with oxygen (apnœic blood); the part *NB* of blood containing nicotine.

FIG. 136.—Shows the effect of opium. In the first part of the tracing the intestine was supplied with apnœic blood; in the latter with blood containing opium.

cork, in a warm chamber. It was supplied with blood by means of a cannula placed in the artery, and allowed to flow out through a cannula in the veins (Fig. 132). Its movements were registered by a small lever placed upon it. When blood fully oxygenated passed through it, the lever traced only a straight line or gently oscillating curve (Fig. 134), but when the flow of blood was stopped, so that the blood stagnated and became venous, contractions began which were indicated as a series of curves. A trace of peptone caused first strong contraction and then a number of irregular contractions, at the same time that the vessels became

fuller of blood (Fig. 134). **Nicotine** causes brisker movements of the intestine, and lessens the rapidity of the flow of blood (Fig. 135). In large doses it causes tetanic contraction of the circular fibres.

Atropine causes irritation of the vessels, while the muscular fibres remain at rest. The action of **opium** is very remarkable; when the tincture is added in the proportion of ·04 to ·01 per cent. to the blood which is circulating through the intestine, the circulation becomes at once lessened, but almost immediately afterwards the diminution passes abruptly into great increase, so that five or seven times as much blood flows through in a given time as formerly; at the same time all the movements of the intestine are abolished, but the intestinal wall instead of being relaxed, as one would expect, is in a condition of considerable contraction (Fig. 136). When the opium is washed out of the vessels by pure blood, the after-effects vary according to the quantity which is used. If it is small, the movements and circulation in the intestine soon become normal, but if a large dose has been used, the circulation returns to the normal condition, but the movements remain abolished for a length of time. The peristaltic action induced by nicotine is arrested by opium. The local action of this drug therefore seems to be that it converts the peristaltic movement into a steady contraction.

A remarkable difference between the action of salts of **sodium** and **potassium** on the intestine has been detected by Nothnagel,[1] and his results have been confirmed by Flöel. When the intestine is exposed, and a potassium salt is applied to its external or peritoneal surface, it produces a contraction of the muscular

FIG. 137.—Represents a piece of duodenum, *a*, after irritation by potassium chloride; *b*, after irritation by sodium chloride. *o* indicates the point of irritation, and the arrows the direction in which the intestinal contents normally move from the pylorus towards the anus. (After Flöel.)

walls, which remains localised to the point of contact, or simply causes a ring of contraction opposite the point (Fig. 137*a*). When a sodium salt is used instead, it produces a contraction which is not limited to the point of contact, but always spreads some little distance from it, and sometimes does so in the direction towards the pylorus, and not towards the anus (Fig. 137*b*), but at other times spreads equally in an upward and downward direction[2] (Fig. 138 *a*). This peculiar action appears to be due to the potassium salts acting as stronger muscular irritants than the sodium salts, while the progressive contraction caused by the sodium is due to the intestinal nerves in their case being to a greater extent involved.

[1] Nothnagel, *Virchow's Archiv*, Bd. 88, p. 1.
[2] Flöel, *Pflüger's Archiv*, vol. xxxv. p. 160.

The effect of **morphine** is very remarkable. When the animal, in addition to being anæsthetised by ether only, as in the previous experiment, has a small dose of morphine injected also into the veins, it has a sedative effect, so that **sodium** salts applied to the intestine produce only a local contraction like potassium salts. But this is only when a certain dose of morphine is employed, about 0·01 to 0·03 gramme of morphine for a rabbit of average size. When the dose was increased from 0·05 to 0·1

FIG. 138.—Represents a piece of intestine, *a*, at the commencement of contraction, after irritation by sodium chloride ; *b* at the end of contraction. *o* indicates the point of irritation. (After Flöel.)

gramme of morphine, an exactly **contrary effect** was produced, and the application of sodium salts, instead of being followed only by local contraction, caused a peristaltic contraction, which was usually very much more energetic than in the normal condition, and not only spread upwards from the point of contact, but downwards towards the large intestine, which it never did under other circumstances.[1] The quieting or inhibitory effect of moderate doses of morphine upon the intestine, irritated by sodium salts, appears to be exercised through the splanchnic nerves, inasmuch as when the mesentery, going to one part of the intestine, is divided in an animal that has received a moderate dose of morphine, the application of sodium salts to this part is followed by a peristaltic wave ; while, in the other parts of the intestine where the nerves are uninjured, the sodium salt still produces only local contractions.

From these experiments it is evident that moderate doses of morphine produce a very different effect upon the intestine from large ones : and this effect has indeed been long recognised in practice.

Moderate doses of opium have a constipating action and are constantly used to check diarrhœa, but large doses, such as those taken by opium-eaters, really have no constipating effect. Indeed, large doses of opium injected directly into the jugular vein of a dog act as most energetic purgatives, being much more prompt in their action than almost any other drug that we know. Immediately after their injection the whole intestinal tract is thrown into violent action and its contents expelled, after which it again becomes quiet.

Very minute doses also seem to have a purgative action, as well as very large ones, and I have used them with considerable success in many cases of constipation.

Constipation may be due to diminished peristaltic action, or

[1] Nothnagel, *Virchow's Archiv*, Bd. 89, p. 1.

diminished secretion, or to both, and in some cases is associated with accelerated absorption. In all probability it is generally due to a diminution in the peristaltic action. In the normal condition this ought to go on regularly, so that the bowels should be evacuated, on an average, once a day, though in some persons evacuations normally occur two or three times a day, and in others only once in three or four days. In some apparently healthy persons I have observed an interval of as much as two or three weeks. In some persons the normal stimulus of ordinary easily digestible food does not seem to be sufficient to keep the bowels acting, but food which leaves much indigestible residue, such as brown or bran bread, salad, figs, prunes, or tamarinds, will do so. These latter fruits owe their laxative properties partly to the insoluble residue they leave and which acts as a mechanical irritant to the intestine, and partly to the salts and sugar and mild laxative principles they contain. Treacle and gingerbread also have a useful aperient action, and their pleasant taste makes them specially suitable for children. The effect of a somewhat stimulant article of food is greater when taken on an empty stomach, and thus a fig before breakfast will have a much greater laxative effect than one taken after dinner. A glass of cold water also, by stimulating peristalsis, will have a laxative action when taken on an empty stomach at bed-time or on rising in the morning. When these means are insufficient a slightly irritating substance, such as an aloetic pill taken on an empty stomach just before dinner, will aid the stimulating effect of the food which is taken afterwards, and will be sufficient to ensure perfectly regular and normal evacuations which do not in any way incommode the person. In consequence of this many people continue to take such **dinner pills** regularly for many years together. Others, again, suffer from constipation, but with them small doses of purgative medicine, if they act at all, act violently, and leave the person weak and uncomfortable, while the bowels again become constipated. This condition is found not unfrequently among women, and is accompanied, sometimes at least, with pain or tenderness in one or both ovaries. In such persons, also, contrary to the general rule, walking exercise increases instead of diminishing constipation.

My friend Dr. Litteljohn noticed that in a case of ovarian tenderness, half a grain of opium given to relieve the pain acted as a purgative. On thinking over this, it occurred to me that the constipation in such cases might be due to reflex irritation of the inhibitory intestinal nerves by the tender ovary. It seemed therefore probable that by using graduated doses of opium, one might be able to lessen the action of the inhibitory nerves, or even to divert the stimulus from them on to the stimulating fibres, and thus produce purgation instead of consti-

pation. Not knowing what dose would be sufficient to produce this effect, I began with one drop of tincture of opium given in a teaspoonful of water every night. To my astonishment this

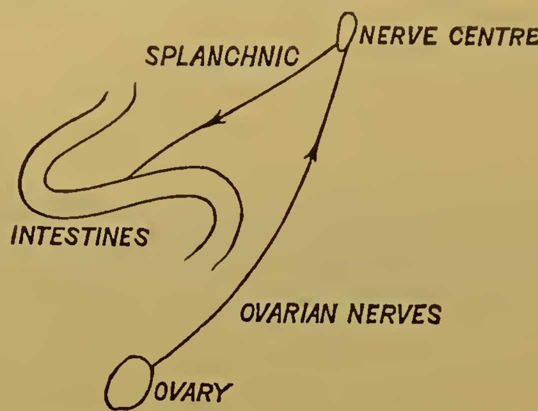

FIG. 139.—Diagram to show the way in which ovarian irritation probably causes constipation.

dose was not only in most cases sufficient, but in one case it proved excessive, doing no good, while half a drop acted as a brisk purgative. It is evident that opium used in this way will not act as a purgative in cases of constipation depending upon general insensibility of the intestinal nerves. The cases in which it is most useful are those of delicate women of a nervous temperament, suffering from ovarian pain, and in whom, ordinarily, purgatives produce excessive action followed by constipation. Small doses of belladonna have also been recommended in constipation, and it is probable that they act in a similar manner when given alone, and that belladonna, hyoscyamus, and essential oils assist the action of purgatives by tending to divert the stimulus, which the irritating constituent of a purgative produces, from the inhibitory to the accelerating intestinal nerves. We know at present but little regarding diminished secretion as a cause of constipation.

Action of Drugs on Absorption from the Intestines.—Ether introduced into the intestine greatly increases its vascularity. It also quickens absorption very much, as is shown by the fact that poison acts more quickly, and such substances as ferro-cyanide of potassium appear sooner in the urine, when they are administered along with ether than when given alone. Carbonic acid has a somewhat similar though weaker action.

Coto bark has been used in diarrhœa, and as it has no proper astringent action, its utility has been ascribed to an antiseptic action by which it diminished the formation of irritant products in the intestines. Albertoni has investigated the action of the coto alkaloids, and finds that although cotoine somewhat lessens putrefaction and the development of bacteria, it does not stop them either in the organism or outside it. It has, however, a very peculiar action on the vessels of the intestine. By keeping up artificial circulation in a loop of intestine (*vide* p. 382), he

finds that cotoine dilates the arteries, causes the blood to flow more readily into the veins, and preserves the vitality of the intestine. It also dilates the vessels of the kidney, and causes the blood to flow more rapidly through them, but does not alter the circulation in the submaxillary gland.

Albertoni thinks that the benefit which cotoine produces in diarrhœa is due to dilatation of the intestinal vessels, and the increased power of absorption which it causes. He considers that in many cases of diarrhœa diminished absorption is a most important factor.[1]

Paracotoine acts like cotoine, but less strongly.

Opium and chloral also dilate the vessels of the intestine, but their action is a paralysing one, while that of cotoine is not.

It is possible that the beneficial action of bael fruit in dysentery may depend on some similar property, as this substance has the peculiarity of acting as a laxative in health, while it lessens the evacuations in dysentery.

Cholagogues probably influence absorption from the intestine powerfully (p. 406).

Intestinal Astringents.—Diarrhœa may depend (1) upon excessive peristaltic action, whereby the contents of the intestine are hurried along before time has been allowed for their absorption, (2) upon diminished absorption, (3) upon excessive secretion. In one form of diarrhœa, where the introduction of food into the stomach seems to excite peristaltic action throughout the intestine so that the person is frequently forced to rise from the table in order to evacuate the bowels, small doses of one half to two minims of liquor arsenicalis given immediately before meals, as recommended by Ringer, frequently act like a charm. In ordinary cases of diarrhœa, opium, by lessening the irritability of the intestine, is most serviceable. Some medicines lessen peristaltic action, not by affecting the bowel, but simply by removing the stimuli which were exciting it. Thus small doses of soda are useful in the diarrhœa of children by neutralising the acid which was acting as an irritant. Creasote has a similar action by lessening putrefaction or fermentation, and thus preventing the formation of irritant products. It is probable that lime acts also to a certain extent by its antacid properties, but there is little doubt that there are other factors in its astringent action which we do not yet understand. The effect of cotoine on intestinal absorption has just been mentioned. With the view of ascertaining whether we could find any drug which would arrest the copious secretion from the intestine which takes place in cholera, Pye-Smith and I made a large number of experiments. For this purpose we isolated loops of intestine, and into one injected sulphate of magnesium mixed

[1] *Archiv für exper. Path. und Pharm.*, vol. xvii. p. 291.

with the drug to be tested. In some experiments we injected the sulphate of magnesium into the intestine, and the drug which we wished to test into the veins.

Sulphate of atropine, iodide of methyl-atropine, chloral-hydrate, emetine, morphine, sulphate of quinine, tannin, and sulphate of zinc, were all tried locally with negative results. Chloral and morphine injected subcutaneously also gave negative results.[1]

FIG. 140.—Diagram illustrating diarrhœa depending on the presence of scybala in the intestine. *a* is a scybalous mass; *b* is the fluid which it causes the intestine to secrete.

In many cases the best way of checking diarrhœa at its commencement is to give a purgative such as castor-oil, either alone or with a few drops of tincture of opium in it. The irritant substances which cause the diarrhœa are swept out of the intestine by the action of the purgative, and any irritation which remains is soothed by the opium. Chronic watery diarrhœa, alternating with constipation, is often best treated in the same way. We may suppose that here the presence of scybalous masses in the intestine gives rise to a watery discharge, which does not, however, wash away the scybala themselves (Fig. 140). When a purgative is given which causes secretion from the intestine above the scybala, the fluid in its downward flow, assisted also by the increased peristalsis, washes away the scybala, and thus removes the source of irritation.

Purgatives.

Purgatives are substances which **cause intestinal evacuations.** They are divided according to their nature into **laxatives, simple, drastic,** and **saline purgatives, hydragogues,** and **cholagogues.**

Laxatives are those which increase only **slightly** the action of the bowels and render the motions slightly more frequent and softer, without causing any irritation. Most articles of food which leave a large indigestible residue in the stomach act as

[1] *Report to Brit. Assoc.*, 1874.

laxatives: such are oatmeal, brown bread, and bran biscuits. Articles of food which contain salts of vegetable acids and sugar in considerable quantity also act as laxatives. The chief laxatives are:—

Honey.	Tamarinds.	Sulphur.
Treacle.	Figs.	Magnesia.
Gingerbread.	Prunes.	Castor-oil (in small doses).
Manna.	Stewed apples.	
Cassia.		

Figs, raspberries, and strawberries, in addition to containing sugar and vegetable acids, have a number of small seeds which are absolutely indigestible, and these have probably a mechanical action in stimulating the bowel.

Simple purgatives also, when given in small doses, act as laxatives: such are carbonate of magnesium, magnesia, olive-oil, and sulphur.

Simple purgatives are more active than laxatives, and their administration is usually followed by one or more copious and somewhat liquid stools. Their action is sometimes accompanied by some irritation and griping. These are:—

Aloes.	Senna.
Rhubarb.	Castor-oil.
Rhamnus (various species), e.g. Frangula and Cascara Sagrada.	

Drastic purgatives are those which cause violent action of the bowels, usually accompanied by evidences of greatly increased peristaltic action, such as borborygmi. They cause irritation of the intestine, and when taken in large doses produce inflammation and symptoms of poisoning. These are:—

Elaterium.	Gamboge.
Colocynth.	Podophyllin.
Jalap.	Croton-oil.
Scammony.	

Saline purgatives consist of neutral salts of metals of the alkalies or alkaline earths. The more commonly employed are:—

Sulphate of potassium.	Bi-tartrate of potassium.
,, sodium.	Tartrate of potassium and sodium.
,, magnesium.	Citrate of magnesium.
Phosphate of sodium.	Sulpho-vinate of sodium.
Tartrate of potassium.	

Hydragogues are purgatives which excite a copious secretion from the intestinal mucous membrane and thus remove much

water from the body; some of them belong also to the drastic group and others to the saline.

Bi-tartrate of potassium.
Elaterium.
Gamboge.

Cholagogue purgatives are those which remove bile from the body. Some drugs aid the removal of bile by stimulating the secretion of the liver, but these, when they have no purgative action, are classed as hepatic stimulants. Cholagogue purgatives probably act by quickening peristaltic action of the duodenum and small intestine, thus preventing the absorption of the secreted bile.

Aloes.	Euonymin.
Rhubarb.	Iridin.
Mercurial preparations (blue pill, calomel, grey-powder).	Podophyllin.

Action of Purgatives.—Purgatives may act in three ways: 1st, by quickening the peristaltic action of the bowels; 2nd, by increasing secretion of the intestinal membrane, and thus to some extent washing out its interior; 3rd, by hindering absorption of the fluids of the intestines.

Simple purgatives act chiefly by stimulating **peristaltic** movements, and have little effect on the secretion.

Hydragogue and **cholagogue** purgatives increase the secretion more than the peristaltic action, and **drastics** increase both. It has been held by several eminent German pharmacologists that the more watery stools produced by many purgatives are due only to more rapid peristaltic action, which hurries along the intestinal contents before there has been time for the absorption of their fluid constituents.

This opinion is chiefly based on the observations of Thiry and Radziejewski.

Thiry isolated a small piece of intestine, one end of which he attached to the abdomen and the other he sewed up. The part of the intestine from which this piece had been removed was again united by sutures, so that the intestine was perfect as before, though rather shorter. The small bag of intestine retained its vascular and nerve supply uninjured and secreted readily when tickled with a feather; but purgative medicines, such as croton-oil, senna, sulphate of magnesium, aloes, jalap, and sulphate of sodium, when applied to it, produced no increased secretion. These experiments led pharmacologists to believe that the ordinary idea that purgatives produced increased secretion from the intestine was erroneous; and the necessity for any such supposition seemed to be removed by an

experiment of Radziejewski, who made an intestinal fistula in the ascending colon of a dog, and found that the intestinal contents as poured into the large from the small intestine exactly resembled the stools which ordinarily follow the administration of a purgative.

The ordinary phenomena produced by purgative medicines would therefore seem to be readily explained by increased peristalsis alone, but some other experiments by Colin and by Moreau have shown that the method employed by Thiry did not afford trustworthy results as to the action of purgatives on the intestines. Moreau isolated three loops of intestine by means of ligatures, carefully emptying the loops beforehand. He then injected a purgative medicine into the middle loop and returned the intestine to the abdomen. On examination some hours afterwards, it was found that, although all three loops had been under similar conditions, the one into which the purgative had been injected was distended with fluid while the others remained perfectly empty. These experiments were repeated by Vulpian, and afterwards by myself, with similar results. There can be no doubt whatever, then, that purgatives act both by increasing peristaltic action and intestinal secretion. Some purgatives act chiefly by the one, and some chiefly by the other.

In the case of some of the salines, the secretion is greatly increased, while the peristaltic movement is so little affected that the secretion may lie so long in the intestine as to be reabsorbed, and the drug therefore fails to produce purgation at all. For this reason it is usual to combine such salines with simple purgatives, which will accelerate the peristalsis.

Laxatives have little action on the system beyond that which is due to the removal of waste and irritating substances from the bowels; but simple purgatives, and still more drastic purgatives, in addition to the direct action upon the bowels, exert an indirect effect upon the blood, removing from it a not inconsiderable portion of its fluid, and therefore causing a form of partial depletion.

The action of cholagogues will be more particularly considered in another paragraph (p. 404).

The action of purgatives generally, and especially of saline cathartics, has been a subject of very great dispute, and it is a matter of extreme difficulty to determine exactly. The question seems to be, however, settled by the masterly researches of Dr. Matthew Hay, and I cannot, I think, do better than give his conclusions in his own words.

1. A saline purgative always excites more or less secretion from the alimentary canal, depending on the amount of the salt and the strength of its solution, and varying with the nature of the salt.

2. The excito-secretory action of the salt is probably due to

the bitterness as well as to the irritant and specific properties of the salt, and not to osmosis.

3. The low diffusibility of the salt impedes the absorption of the secreted fluid.

4. Between stimulated secretion on the one hand, and impeded absorption on the other, there is an accumulation of fluid in the canal.

5. The accumulated fluid, partly from ordinary dynamical laws, partly from a gentle stimulation of the peristaltic movements excited by distension, reaches the rectum and produces purgation.

6. Purgation will not ensue if water be withheld from the diet for one or two days previous to the administration of the salt in a concentrated form.

7. The absence of purgation is not due to the want of water in the alimentary canal, but to its deficiency in the blood.

8. Under ordinary conditions, with an unrestricted supply of water, the maximal amount of fluid accumulated within the canal corresponds very nearly to the quantity of water required to form a 5 or 6 per cent. solution of the amount of salt administered.

9. If, therefore, a solution of this strength be given, it does not increase in bulk.

10. If a solution of greater strength be administered, it rapidly increases in volume until the maximum is attained. This it accomplishes in the case of a 20 per cent. solution in from one hour to one hour and a half.

11. After the maximum has been reached, the fluid begins gradually and slowly to diminish in quantity.

12. *Cæteris paribus*, the weaker, or in other words, the more voluminous the solution of the salt administered is, the more quickly is the maximum within the canal reached; and accordingly purgation follows with greater rapidity.

13. Unless the solution of the salt is more concentrated than 10 per cent. it excites little or no secretion in the stomach.

14. The salt is absorbed with extreme slowness by the stomach of the cat.

15. The salt excites an active secretion in the intestines, and probably for the most part in the small intestine, all portions of this viscus being capable of yielding the secretion in almost equal quantities.

16. The bile and pancreatic juice participate but very little in the secretion.

17. The secretion is probably a true *succus entericus*, resembling the secretion obtained by Moreau after division of the mesenteric nerves.

18. The secretion is promoted by local irritation of the intestine, as by ligatures, but only in the immediate vicinity of the irritation.

19. Absorption by the intestine generally is reflexly stimulated by such irritation (the effect of numerous ligatures applied at points remote from the seat of the injected salt being to diminish the amount of purgative fluid by accelerated absorption).

20. If the salt solution be injected directly into the small intestine, the stronger within certain limits the solution is, the greater will be the accumulation of fluid within the intestine.

21. This difference is not observed when the salt is administered *per os*, as the strong solution becomes diluted in the stomach and duodenum before passing into the intestine generally.

22. The difference is due to the local action of the salt on the mucous membrane, and probably more to an impeded absorption than to a stimulated secretion.

23. When the salt is administered in the usual manner, it appears, in the case of the sulphate of magnesium and sulphate of sodium, to become split up in the small intestine, the acid being more rapidly absorbed than the base.

24. A portion of the absorbed acid shortly afterwards returns to the intestines.

25. After the maximum of excretion of the acid has been reached, the salt begins very slowly and gradually to disappear by absorption, which is checked only by the occurrence of purgation.

26. During the alternations of absorption and secretion of the acid, it is the salt left within the intestine which excites secretion, the absorbed and excreted acid exerting no such action whilst in the blood, or during the process of its excretion, as Headland believed.

27. The salt does not purge when injected into the blood, and excites no intestinal secretion.

28. Nor does it purge when injected subcutaneously, unless in virtue of its causing local irritation of the abdominal subcutaneous tissue, which acts reflexly on the intestines, dilating their blood-vessels, and perhaps stimulating their muscular movements.

29. The sulphate of sodium exhibits no poisonous action when injected into the circulation.

30. The sulphate of magnesium is, on the other hand, powerfully toxic when so injected, paralysing first the respiration and afterwards the heart, and abolishing sensation or paralysing the sensory-motor reflex centres.

31. Both salts, when administered in the usual manner, produce a gradual but well-marked increase in the tension of the pulse.

32. According as the salt-solution within the intestine increases in amount there occurs a corresponding diminution of the fluids of the blood.

33. The blood recoups itself in a short time by absorbing from the tissues a nearly equal quantity of their fluids.

34. The salt, after some hours, causes diuresis, and with it a second concentration of the blood, which continues so long as the diuresis is active.

35. As the intestinal secretion excited by the salt contains a very small proportion of organic matter as compared with the inorganic matter, the purgative removes more of the latter than the former from the blood. In certain cases a large quantity of the salts of the blood is thus evacuated.

36. The amount of the normal constituents of the urine is not affected by the salt.

37. After the administration of sulphate of magnesium much more of the acid than of the base is excreted in the urine.

38. The salt has no specific action in lowering the internal temperature of the body, or has it only to a very small extent.

39. It reduces, however, the absolute amount of heat in the body.

Uses.—Purgatives are used, firstly, to **remove** from the intestinal tube **fæcal** matters. They thus not only prevent the accumulation of such matters, but remove the irritation which their presence produces, and which may evidence itself in disturbances of other organs, producing, for example, headache and malaise. These disagreeable symptoms produced by constipation are perhaps partly due to the irritation of the intestinal nerves producing reflex disturbance of the circulation, but it is probable also that they may be due in part to the toxic action of poisonous gases, liquids, or solids, generated in the intestine by imperfect digestion or decomposition of the food. For such purposes as this we may employ, as we find them necessary, laxatives or simple purgatives.

The second use of purgatives is to **remove liquid** from the body in cases of dropsy, due either to heart or kidney disease. For such purposes we use saline hydragogue cathartics.

From his researches on the action of saline cathartics Dr. Hay had found that if a salt be given in a concentrated solution when the alimentary canal contains little or no fluid, it produces an almost immediate and very decided concentration of the blood by the removal of a large quantity of its water in the form of intestinal secretion. But if the salt be given in sufficient water, or if the alimentary canal contain sufficient fluid at the time of administration, no such concentration occurs. The concentration reaches its maximum in half an hour, but does not last more than half an hour or an hour, when it begins to decline, and continues to do so until it reaches the normal at the end of about four hours. This return of the blood to its normal concentration is not due to re-absorption from the intestine, but to the absorption of lymph and fluids from the tissues. Some hours after the administration, either of a concentrated or dilute saline solution, the blood undergoes another concentration, less

than the first but continuing longer. Saline cathartics, as often used in dilute saline solution, owe their use in dropsy, to a great extent, to their diuretic action. When given in concentrated solution under proper conditions, the benefit they produce by purgation is exceedingly great. These conditions are that the alimentary canal should be freed from food and especially from liquids by previous abstinence for some hours, and that the salt should be given along with the smallest possible quantity of water. Sulphate of magnesium being soluble in less than its own weight of water is most suitable. Alkaline tartrates, and Rochelle salt may also be useful; sulphate of sodium is more insoluble, and therefore less suitable; phosphate of sodium and sulphate of potassium are too insoluble to be of any service.[1]

The third use is to lower the temperature in fever, and for this we chiefly use salines. The *modus operandi* here is not yet well understood, as they have no such action in health (p. 394).

The fourth use is to lower the blood-pressure, and thus to prevent the rupture of a blood-vessel, and consequent apoplexy, or to prevent further extravasation in a case where the vessel has already burst.

The regular use of aperients is especially necessary in gouty persons with contracted kidney and high blood-pressure. How far their utility is to be ascribed to their direct effect in lowering the blood-pressure, and how far to the removal of waste products which might raise the pressure it is impossible at present to say. The utility of purgatives after apoplexy has occurred may be doubtful, and though usually administered, they probably do no good. But, even if they do no good, they do no harm. A drop of croton-oil or a few grains of calomel on the tongue is the usual form of administration.

A fifth use is to prevent straining at stool where violent efforts are dangerous, as in aneurism, hernia, &c.

Action of Irritant Poisons.

A great number of drugs which are employed in medicine, and are most useful when given in small doses, act as irritant poisons in large ones. Their action is then not restricted to the stomach, nor even to the whole of the intestinal canal, but they exercise, in addition, a marked effect upon other functions of the body, such as respiration and circulation.

In considering the physiological action of many drugs it is necessary to describe the effect they will produce when given in large quantities, as, for example, in an overdose, as well as in moderate or small ones.

It will save both time and space to consider here the action

[1] *Lancet*, April 21, 1883.

of irritant poisons generally, and to refer to this description when discussing the effect of individual drugs.

The symptoms of irritant poisoning are to a great extent the same, whatever be the irritants swallowed; it is therefore convenient to give an account of these symptoms, and then to mention the special peculiarities which occur in the case of different poisons.

A poison is most usually swallowed, and it then comes successively in contact with the lips, **mouth** and tongue, **gullet** and **stomach.** It may sometimes reach no farther, being either evacuated by vomiting or absorbed. It frequently, however, also passes into the **intestine.** On all those parts which it reaches it exerts a local action; besides this, however, it exerts a reflex action on the respiration and circulation. Corrosive poisons produce a feeling of burning in the lips, mouth, gullet, and stomach; the **pain** in the stomach, extending more or less over the abdomen, is accompanied by tenderness, and is increased by pressure. It is thus distinguished from the pain of colic, which is usually relieved by pressure.

The irritation of the stomach gives rise to **vomiting**; the vomited matters usually consisting, first of the contents of the stomach, next of bile or mucus, and lastly of mucus stained

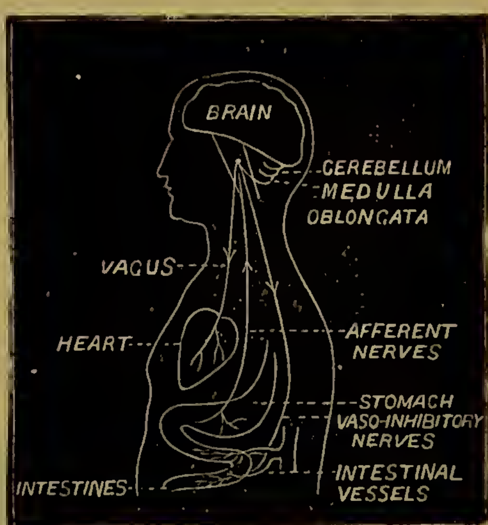

FIG. 141.—Diagram to show the nervous mechanism by which the action of the heart may be depressed by irritation of the stomach. The reflex irritation of the vagus may render the heart's action simply weak, or slow and weak (*vide* p. 310).

with blood. These matters may sometimes be more or less acted upon by the poison, where this is a strong acid or alkali. The intense irritation in the stomach produces effects on the respiration and circulation very much like those caused by a severe blow in the epigastrium. The heart's action is greatly weakened at first, and it may be rendered slow from reflex irritation of the vagus, but in the later stages it is generally rapid, very small, weak, or almost imperceptible; sometimes it may be intermit-

tent (see Fig. 141). On account of the weakness of the circulation the face and the general **surface** of the body are pale, the cheeks sunken, and the extremities cold. The frequency of the **respiration** may vary, may be either slower or quicker than normal, but it is almost always laboured and shallow, as the intense irritation in the stomach renders the descent of the diaphragm in deep inspiration painful, and the sufferer therefore tries to avoid it.

Although the **pulse** at the beginning of the poisoning may be slow, when advanced it is usually, as already mentioned, very rapid. Exceptions to this rule may occur, chiefly in the case of poisons which, after their absorption, have an action on the heart itself; these are potassium nitrate and salts of barium. In consequence of the weakness of the circulation the face is usually very pale, but an exception to this may occur in poisoning by corrosive sublimate, where the face may be flushed. In arsenical poisoning the face is not only pale, but assumes a bluish hue, and the pinching may be extreme, so that the condition resembles that of a person suffering from Asiatic cholera.

Where the poison is exceedingly corrosive, as in the case of acids and caustic alkalies, its local action on the stomach in causing swelling of the mucous membrane may tend partially to occlude the pylorus, and the greater part of the poison may either remain in the stomach itself or be ejected by vomiting without passing into the intestine. In such cases vomiting will occur alone without being accompanied by purging, and the pain in the abdomen may be less diffused. Most irritant poisons, however, pass from the stomach into the **intestines**, and thus violent purging is induced in addition to the vomiting. The inflammation of the intestines also causes the pain to be diffused over the whole abdomen.

Peculiarities in the Action of different Irritant Poisons.—Acids throw down albumen as a white precipitate, and in consequence, when brought in contact with the lips or tongue in a concentrated condition, they cause white stains. The white stain is most marked in the case of carbolic acid; it occurs also from hydrochloric acid; it may occur from sulphuric, but as the further action of the sulphuric is to char albumen or other organic substances, the stain may acquire a brown or black colour. Nitric acid produces a yellow stain, rendered brighter by the application of ammonia. Perchloride of iron produces a yellowish-brown stain; the caustic alkalies remove the epidermis and give a soapy feeling to the surface, but do not leave any stain. After a short time the mucous membrane becomes injected and swollen from the irritation.

In the mouth the taste peculiar to the poison often leads to its detection, so that very little of it may be swallowed in cases

where a person was about to take it unwittingly. Arsenic, although a powerful irritant in the stomach, is almost tasteless.

As the poison passes down the gullet, it may have an important influence on the respiratory tract; this is especially the case where it gives off fumes like nitric acid, hydrochloric acid, and ammonia; the fumes, passing into the larynx and trachea, excite irritation, spasm, and inflammation, and may cause death by suffocation. Death by suffocation may, however, sometimes occur from the action of poisons which do not fume, e.g. sulphuric acid; the local irritation producing such great œdema and reflex spasm about the epiglottis as to cause obstruction to the respiratory passages. Sometimes, also, such poisons as sulphuric acid may pass directly into the trachea instead of the œsophagus, and thus cause very rapid death from suffocation.

Purging is usually absent and the bowels constipated in poisoning by strong alkalies or acids, and by salts of lead; the former probably act by corroding the stomach, and partially occluding the pylorus; the latter by lessening the peristaltic movements of the intestine. In the case of lead salts the abdominal pain differs from that of ordinary irritant poisons, being of a colicky nature, and to a certain extent relieved by pressure.

Secondary Effects of Irritant Poisoning.—After the immediate condition of collapse caused by the powerful action of the irritant has passed off, the local inflammation which it has produced may give rise to a general febrile condition, with hot skin, flushed face, and quick bounding pulse. This condition may be accompanied by other symptoms due to the physiological action of the poison after its absorption; thus in the case of corrosive sublimate, there may be the metallic taste, sore gums, and profuse salivation characteristic of mercurial poisoning.

One of the most important instances of the secondary effects of irritant poisons is phosphorus; after the primary symptoms of gastric irritation have passed off the patient may appear perfectly well, and then vomiting and purging may set in a second time. These are due, not to the local action of the phosphorus which has been swallowed on the stomach and intestines, but to the changes in the liver, blood, and other organs, which the phosphorus has produced after its absorption. A similar condition has been observed in poisoning by arsenic, but usually the symptoms of arsenical poisoning are continuous, and do not exhibit a distinct intermission of this kind.

Death may occur from the secondary action of some poisons a good while after the primary symptoms have disappeared; thus strong acids and alkalies may produce death, weeks or even months after they have been swallowed, from the effects of their local action on the œsophagus or the stomach. During the passage down the œsophagus they may destroy the mucous

membrane to such an extent that when it heals and the cicatrix begins to contract, the lumen of the tube may be completely obstructed, so that no food can reach the stomach, and the patient dies of starvation; or the mucous membrane of the stomach may be destroyed to such an extent that what remains is insufficient to digest the food, and the patient dies from non-assimilation.

ACTION OF DRUGS ON THE LIVER.

The liver is by far the largest organ in the body, and it is placed in a very peculiar situation. It acts as a porter or door-keeper to the circulation, all the substances which are absorbed from the intestinal canal having to pass through the portal vein and the capillaries of the liver before they can enter the general circulation.

Since the discovery by Ludwig and Schmidt-Mülheim that peptones are poisonous when injected directly into the circulation, the liver has acquired a new importance. Schiff and Lautenbach indeed had previously made some experiments which they thought showed that a subtle poison existed in the blood even of healthy animals, but was destroyed by the liver. They based this idea on the observation that ligature of the portal vein causes death in animals with very much the same symptoms as when they are bled to death. Ludwig had formerly explained this phenomenon by supposing that the ligature caused the blood to accumulate in the large and dilatable portal radicles and prevented it from getting into the general circulation again. The animal was thus, as Ludwig expressed it, bled to death into its own veins. Schiff and Lautenbach, however, thought the symptoms were due rather to poison than to this mechanical alteration in the circulation, because they found that when the blood of an animal whose portal vein had been ligatured was injected into a frog, it produced death within three hours, whereas blood from a similar animal whose portal vein had not been ligatured produced no effect.

The **liver** therefore seems to have a most important function in **destroying** the **poisonous properties** of **peptones**, and perhaps **other substances** produced during digestion, and possibly also of poisonous products of tissue-waste. The peptones are converted by it into sugar and glycogenic substance.[1]

Drugs which act on the liver are usually divided into hepatic stimulants and cholagogues, and into hepatic depressants.

It has been for a very long time a matter of clinical experience that the administration of mercurial purgatives was frequently followed by the discharge of greenish bilious-looking evacuations

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[1] Seegen, *Pflüger's Archiv*, xxviii. p. 990.

and a great improvement in the general condition of the patient. These two results were classed together as cause and effect, and the improvement was considered to be due to the removal of bile. It was then supposed that the bile was formed in the blood and

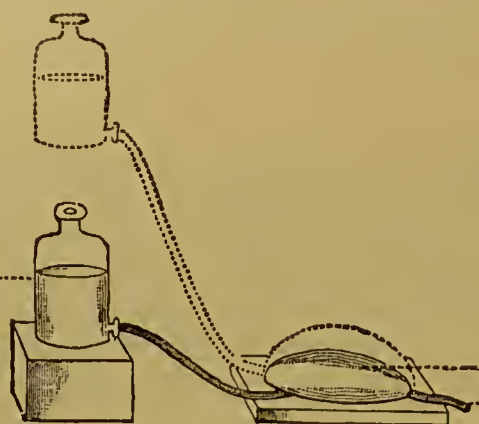

FIG. 142.—Diagram to show the effect of artificial circulation of blood through the liver, under different pressures. The continuous lines indicate the size of the liver, and the arrangement of the apparatus during circulation, under a low pressure. The dotted lines indicate the increased size of the liver, and the arrangement of the apparatus, under a high pressure.

simply excreted by the liver, and, therefore, the bilious-looking stools were ascribed to stimulation of the secreting function of the liver by the mercurials. Hepatic stimulants and cholagogues were therefore considered to be identical. We now know that the bile is formed in the liver and not simply excreted by it from the blood, and that bile formed in the liver may again be absorbed into the blood. Increased functional activity of the liver might thus lead to the presence of a greater instead of a less quantity of bile in the blood. Recent experiments have also shown that one of the most marked cholagogues which we know, viz. calomel, appears rather to diminish than to increase the actual secretion of bile, so that we are now obliged to distinguish between hepatic stimulants and cholagogues. **Hepatic stimulants** are drugs which increase the functional activity of the liver, and the amount of bile which it forms. **Cholagogues** are substances which remove bile from the body, possibly by acting rather on the intestines; they do not necessarily increase the secretion of bile, they may only prevent its re-absorption and thus diminish the quantity in the circulation. **Hepatic depressants** are drugs which lessen the quantity of bile secreted by the liver.

In relation to tissue-waste it is not to be forgotten that the products of the functional activity of one organ are not only poisonous to itself, but may be poisonous to other organs. Thus the waste products of muscular activity gradually poison the muscle and prevent its contraction, although as soon as they are washed out with salt solution the muscle recovers its power.

Lactic acid also, which is a product of muscular waste, is poisonous not only to muscle but to some extent to nerves, and

lessens the functional activity of the brain and produces sleep. At the same time it is possible that these waste products, poisonous in themselves, may through slight changes be rendered available for nutrition, just as peptones which are themselves poisonous are most important foods.

Besides acting on peptones, the liver seems to have the power of destroying the poisonous properties of some **vegetable alkaloids**. For example, $\frac{1}{20}$th of a drop of nicotine given to a frog does not produce death, but $\frac{1}{40}$th is sufficient, when the liver has been previously removed. Coniïne, cobra poison and hyoscyamine, all exert much less poisonous action after they pass through the liver, before they reach the general circulation, than they do when injected directly into the blood. Curare, prussic acid, and atropine, on the other hand, do not have their action modified.[1]

The result of these experiments may be partly explained on the supposition that a good deal of the **poison** has been **excreted** along with the bile, and has thus been prevented from reaching the general circulation. But it is probable that in addition to the function of excreting poisons, the liver has also got the power of destroying poisons, and, it may be, the power of removing poisons from the circulation by merely storing them for a time.

In relation to this subject it is interesting to bear in mind that alkaloids to which the name of ptomaïnes has been given (p. 99), are formed in dead bodies during the process of decomposition, and that when a solution of peptone is treated with potash and ether it yields a body which appears to be a volatile alkaloid. If putrid peptone is treated in the same way, a solid, non-volatile alkaloid is obtained.[2]

Ptomaïnes are not only formed in dead bodies, they are also formed in the intestine by the decomposition of parts of its contents. They have been found in large quantities by Bouchard both in the stools of persons suffering from diarrhœa or typhoid fever, and in normal fæces. They appear to be absorbed from the intestine into the blood and excreted by the urine. They have been found by Bouchard in the urine both in health and disease, and Bocci has shown that the human urine has a paralysing action on frogs like that of curare, or of the ptomaïnes which Mosso and Guareschi have obtained from putrefied fibrin or brain.

Some time ago I pointed out[3] the resemblance between the languor and weakness which occur in many cases of indigestion and the symptoms of poisoning by curare, and drew attention to

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[1] Lautenbach, *Philadelphia Medical Times*, May 26, 1877.

[2] Tanret, *Comptes Rendus*, xcii. 1163.

[3] Lauder Brunton, 'Indigestion as a Cause of Nervous Depression,' *Practitioner*, vol. xxv. October and November 1880.

the probability that the languor was due to the effect of poisonous substances absorbed from the intestine. These I considered to be probably peptones, but it is possible that they may be ptomaïnes. But whether the poisonous substances be peptones or ptomaïnes, the function of the liver is equally important in preventing them from reaching the general circulation.

Bearing in mind, then, the office of the liver as a porter to prevent the passage of injurious substances from the intestinal canal into the blood, and the great effect that any alteration in the circulation through it may produce upon the circulation, and consequently on the functions of all the intestinal organs, we shall much more readily understand the importance of this gland, the largest in the body, than if we look upon it simply as an instrument for secreting the bile which plays a useful, but still subordinate part in the process of digestion.

We are still but imperfectly acquainted with its functions, but we may say that they are at least five :—

1st, to **form** and **store up glycogen**, a material which will afterwards be used in evolving heat and muscular energy; it will thus, as it were, perform the office of a kind of coal-bunker to the body;

2ndly, to **secrete bile** for use in digestion;

3rdly, to **excrete bile**;

4thly, to **destroy peptones** which are poisonous when they are directly introduced into the general circulation, and to convert them into glycogen, &c.;

5thly, to **destroy** or store up and **excrete** other organic **poisons** which may have been formed in the alimentary canal during the process of digestion, or may have been introduced into it from without.

The **glycogenic function** of the liver is influenced by a number of drugs, especially phosphorus, and substances belonging to the same chemical group. Phosphorus, arsenic, and antimony, all destroy the glycogenic function, and at the same time tend to cause fatty degeneration of the organ. It is possible that these effects of the poisons are closely connected, but the exact connection between them has not yet been ascertained.

In consequence of the disappearance of glycogen from the liver which is caused by these drugs, puncture of the fourth ventricle will no longer cause glycosuria in animals which have been poisoned by them. Attempts have been made to utilise this fact in the treatment of diabetes, but as yet the results have not been very satisfactory.

Hepatic Stimulants.—The action of drugs on the **secretion** of the liver has been very carefully studied by some observers, especially by Röhrig, Rutherford, and Vignal. The mode of experimenting was to curarise a dog, ligature the common bile-

duct and insert a cannula into it. The bile was thus entirely prevented from reaching the intestine, and the whole of it flowed through the cannula into a vessel in which it was collected, so that the amount secreted in a given time was readily estimated. The drug was then administered, usually by injection into the duodenum, and the increase or diminution which this caused in the bile was noticed.

The ingestion of **food** greatly **increases** the secretion of bile, and in order to get rid of this disturbing factor, the experiments were all made on fasting animals.

A great number of drugs were experimented upon, some of which were found to stimulate the liver, and increase the quantity of bile without altering its quality, so that their action upon the liver would be nearly analogous to that of laxatives upon the intestine; others increased the quantity of bile, and rendered it more watery; others again had little effect upon the liver, but stimulated the intestinal secretion and movements.

The following are hepatic stimulants:—

Acid, dilute nitro-hydro-chloric.[1]	Ammonium benzoate.[2]	Podophyllin.[1]
Aloes.[1]	Baptisin.[2]	Sanguinarin.[1]
Rochelle salt.[3]	Euonymin.[1]	Colchicin.[1]
Sodium sulphate.[2]	Hydrastin.[2]	Colocynth.[1]
Sodium phosphate.[1]	Juglandin.[2]	Jalap.[2]
Potassium sulphate.[2]	Iridin.[1]	Rhubarb.[2]
Mercuric chloride.[1]	Leptandrin.[2]	Ipecacuanha.[1]
Sodium salicylate.[1]	Phytolaccin.[1]	Physostigma[3] (extract).
Sodium benzoate.[1]		

Those drugs which stimulate the intestine much, as a rule increase only slightly the secretion of bile by the liver, and podophyllin, which in certain doses acts as a powerful hepatic stimulant, ceases to have this effect when it produces marked purgation. These effects occur independently of the action of the drugs on the re-absorption and re-secretion of bile, inasmuch as in the experiments quoted the whole of the bile was collected directly from the liver and not allowed to pass at all into the intestine. A large number of substances belonging to the aromatic series act powerfully on the liver. Some of them, like salicylate of sodium, greatly increase the watery constituents of the bile, so that it is not only more abundant, but much more dilute than normal. Others of them, e.g. toluylendiamine, increase the solids to such an extent that the bile becomes so viscid that it cannot flow through the bile-ducts, and being absorbed gives rise to jaundice. A number of bitters belong to the aromatic series (p. 364).

[1] The most powerful stimulants in the preceding list are indicated by ([1]), the less powerful by ([2]) and ([3]).

It seems not improbable that by further observations many aromatic compounds may be arranged in a regular series, according to their action on the solid and liquid constituents of the bile.

Cholagogues.—In making experiments, similar to those of Rutherford and Vignal, Schiff observed that the secretion of bile was very much greater for a short time immediately after the bile-duct was tied, than it was later on; and on further investigation he found that this was due to the fact that the liver

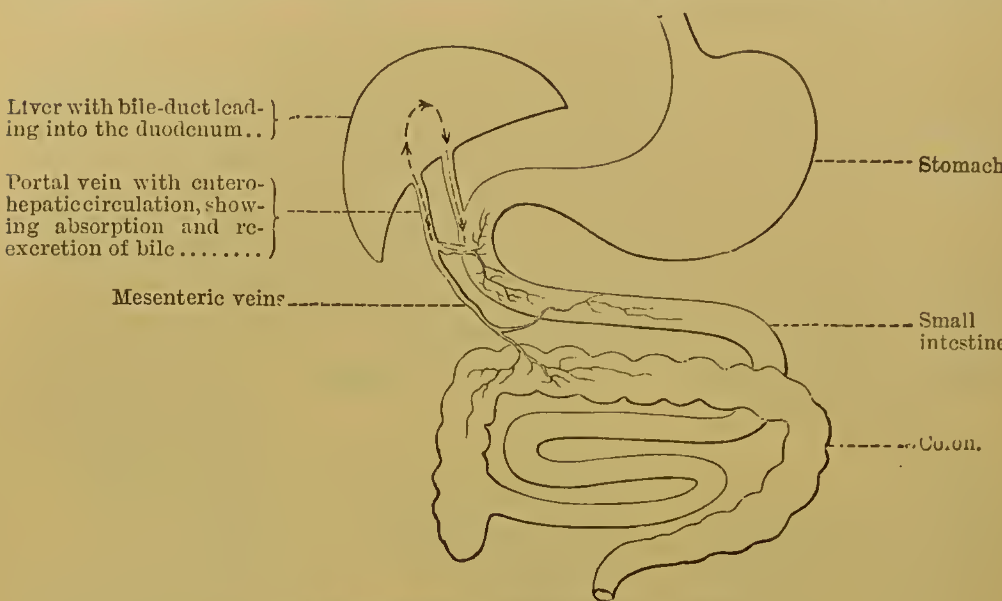

FIG. 143.—ENTERO-HEPATIC CIRCULATION.

has a double function; it not only **forms new bile**, but **re-excretes** the **old bile** which has been re-absorbed from the intestine. A certain quantity of bile is lost in the fæces, but a considerable portion of it seems to be utilised again and again; being formed by the liver, poured out into the intestine, re-absorbed and again excreted. This circulation of bile between the intestine and the liver has been called by Lussana the entero-hepatic circulation (Fig. 143). It has been shown that the bile which is absorbed from the duodenum does not merely act as a stimulus to the liver to cause a greater formation of new bile, but is actually re-excreted, by injecting ox-bile, which gives Pettenkofer's reaction, into the duodenum of a guinea-pig, and finding that shortly afterwards the bile which issued from the gall-duct gave this reaction while the bile normally secreted by the guinea-pig does not.

Not only is bile re-excreted in this manner by the liver, but other substances also, such as **medicines** and **poisons**, are likewise **excreted.** The absorption and re-excretion take place with great rapidity, for Laffter, in some experiments made under Heidenhain's direction, found that rhubarb injected into the duodenum appeared in the bile in less than five minutes. Sub-

stances injected into the blood were also excreted by the bile with great rapidity, so that sulphindigotate of sodium, introduced directly into the circulation in some experiments, began to colour the bile blue one minute after its injection. Other substances are also absorbed from the intestine and excreted by the liver and passed round in the entero-hepatic circulation, just like the bile. Curare is one of these, and to this probably is due in a great measure the absence of fatal effect from its introduction into the stomach. **Iron** also circulates with the bile, and it is probable that the beneficial effect of large doses may be due in part to the action of the iron upon the liver. The objection has been raised to the employment of large doses that they are useless, inasmuch as the whole of the iron which is taken into the mouth is again expelled in the fæces, but there can be no doubt that clinically large doses of iron are sometimes beneficial. Copper and manganese also appear in the bile, and it is probable that lead and all the heavy metals pass chiefly out of the body by this channel. For the action of the liver on **alkaloids** see p. 401.

It has been suggested by Lussana that the **malarial poison** also circulates in the entero-hepatic circulation.

From the fact that bile is re-absorbed from the intestine, it is obvious that an **hepatic stimulant** which simply increases the secretion of the bile by the liver, **will not of itself act as a cholagogue** and remove the bile from the body. In order to do this, this action must be combined with increased peristaltic action of the bowels, which will hurry the bile out and prevent its re-absorption. If, in addition to increased peristalsis, we have increased secretion from the intestinal mucous membrane, so as to wash out the intestine, we shall get the bile still more effectually removed from the body. The necessity for such a combination has indeed been long ago shown by clinical experience, and the advantages of following a mercurial pill by a saline purgative in order to clear it away have long been recognised. Some hepatic stimulants increase also the peristaltic movements and secretions from the intestine—for example, those substances which have been already enumerated as cholagogue purgatives.

Aloes.	Colocynth.	Sulphate of potassium.
Baptisin.	Jalap.	Sulphate of sodium.
Colchicum in large doses.	Podophyllin.	Phosphate of sodium.
	Rhubarb.	Mercury salts.

In most cases, however, it is advisable to **combine hepatic and intestinal stimulants** in order to ensure a more complete **cholagogue effect.** Thus calomel as employed in Rutherford's experiments has no stimulant action on the liver, but stimulates the intestinal glands; corrosive sublimate, on the contrary,

stimulates the liver powerfully but has a very feeble stimulant action on the intestine; a combination of the two stimulates both the liver and the intestinal glands. When used in medicine, calomel is recognised to be a powerful cholagogue, one of the most powerful indeed that we possess, and it is by no means impossible that a small portion of it may be converted into corrosive sublimate in the intestine, so that we thus get from the calomel, when given alone, the combined effects of both the mercurial preparations just mentioned. It is more probable, however, that the cholagogue action of calomel is due to its having a peculiar stimulant action on the duodenum and ileum, so as to hurry the bile along the intestine and prevent its re-absorption. The reason for supposing that this is the case rather than that part of it is converted into corrosive sublimate and stimulates the liver, is that when given to dogs with a permanent fistula it does not increase the flow of bile, which it would probably do if any corrosive sublimate were formed. Another is that after the administration of calomel, leucin and tyrosin, which are products of pancreatic digestion, are found in the stools, and it seems not improbable that their appearance under such circumstances is due to their having been hurried along the intestine from the duodenum to the anus, and evacuated without time being allowed for their absorption or decomposition in the intestine.

Adjuncts to Cholagogues.—The pressure under which bile is secreted is very low, so that a very slight obstruction to its flow through the common bile-duct is sufficient to cause its accumulation in the gall-bladder and gall-ducts, and thus to lead to its re-absorption. This is readily observed in cases of catarrh, either of the duodenum or of the gall-ducts. In such cases the use of ipecacuanha is indicated. This drug has been found clinically to be of great service, and it probably acts by lessening the tenacity of the mucus in the gall-duct, and thus tends to remove the obstruction in front, while at the same time it increases the pressure behind, by stimulating the hepatic secretion. The movements of the **diaphragm** have a powerful action in aiding the **expulsion** of **bile** from the liver; they do this to a certain extent in ordinary respiration, but their effect is much greater in forced inspiration. Exercise therefore tends to expel bile from the liver, and prevent its accumulation in the biliary capillaries, but a little **brisk exercise** as in riding, rowing, climbing, tennis, &c., will have in a few minutes a more beneficial action than a lazy constitutional walk of a couple of hours.

The secretion of bile is not only increased, but the **pressure** under which it is secreted is **raised** by **sipping fluids.** This is, in all probability, due to nervous influence, for it has been shown by Kronecker that taking a liquid in numerous small sips will for the time completely abolish the inhibitory action of the vagus

on the heart. It is probably in consequence of this fact, that Carlsbad water, when taken in numerous sips for an hour or more, as at Carlsbad itself, is so exceedingly efficacious in hepatic diseases, while sodium sulphate, which is the main constituent of the water, was found by Rutherford to have only a very slight action as a stimulant to the liver.

Uses of Hepatic Stimulants and Cholagogues.—The pressure under which the bile is secreted is very small, but the blood-pressure also in the portal vein is very low. In consequence of this a very slight increase in the tension of the bile within the gall-ducts, or diminution of the pressure of blood in the vein, causes the bile to be absorbed. It is then carried by the circulation to various parts of the body and disturbs their functions. It lessens the power of the heart and appears to diminish the activity of the brain, so that persons suffering from biliousness and presenting a slight icteric tinge of the conjunctiva, are apt to feel irritable, stupid, and out of sorts generally. Cholagogues are useful by removing bile from the body, and thus relieving the symptoms above mentioned. It is probable, however, that they also in some way improve the portal circulation, and thus lessen congestion of the stomach and intestines, as in Beaumont's experiments on Alexis St. Martin (p. 369).

Hepatic Depressants.

Purgatives will act as hepatic depressants and lessen the secretion of the liver by removing from the intestine the bile which would otherwise be re-absorbed, and by hurrying out also the food which might yield materials for the secretion of new bile; but some substances, such as calomel, castor-oil, gamboge, and magnesium sulphate, were found by Rutherford to depress the secretion in cases where the bile-duct was ligatured and the animals fasting, so that in all probability the effect of the drugs in diminishing the secretion was due to their lowering the blood-pressure in the liver.

Action of Drugs on the Pancreas.

The pancreatic juice is important in the process of digestion, as it has the threefold power of converting starch into sugar, of digesting proteids with the formation of peptones, and of splitting up and emulsifying fats.

The process of secretion in the pancreas is associated with increased blood-supply as in other glands. Its nerves arise from the hepatic, splenic, and superior mesentery plexuses, with branches from the vagi and splanchnics. Electrical stimulation of the gland itself will cause secretion, and so will stimulation of

the medulla oblongata. It is arrested by powerful irritation of sensory nerves, such as the central end of the vagus, the crural, or sciatic, and by the production of nausea or vomiting.

The secretion is stimulated by the injection of ether into the stomach, and appears to be paralysed by atropine in the same way as the secretion of the salivary gland.

When fibrin is digested with pancreatic juice the solution soon begins to swarm with bacteria, and products of decomposition occur, among which is indol with a peculiarly disagreeable odour.

When calomel is added to pancreatic juice, it does not impair its digestive action upon starch, proteids, or fats, but it arrests decomposition, and thus prevents the formation of indol and scatol, although leucin and tyrosin, which are normal products of pancreatic digestion, are still formed. Salicylic acid has a similar action.[1]

After the administration of calomel the stools are often of a green colour, and this is due to unaltered bile. From the experiments on biliary fistulæ already mentioned it is probable that this bile in the motions is not due to increased secretion by the liver, but to the occurrence of diminished absorption, caused by its more rapid passage through the intestine, and possibly also to lessened transformation from the effect of the calomel in preventing its decomposition.

Anthelmintics.

These are remedies which kill or expel intestinal worms.

They have been divided into **vermicides**, which kill the worm, and **vermifuges**, which expel the worm without necessarily killing it, e.g. purgatives.

The chief worms which infest the intestine are tape-worms, round-worms, and thread-worms.

The chief Vermicides are :—

For Thread-Worms.—Local injections of alum, iron, lime-water, quassia, eucalyptol, sodium chloride, and tannin or substances containing it, as catechu, hæmatoxylon, kino, rhatany.

For Round-Worms.—Santonin, santonica.

For Tape-Worms.—Areca nut, filix mas, kamala, kousso, pomegranate, pelletierine, turpentine, chloroform.

As Vermifuges.—Castor-oil, scammony, rhubarb.

Adjuncts.—Ammonium chloride, common salt and iron, and bitter tonics, are useful internally in preventing excessive secretion of intestinal mucus, which affords a **nidus** for intestinal worms.

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[1] *Zeitschr. f. physiol. Chem.*, vi. 2.

Uses.—They are used to destroy and remove worms present in the intestine. In order that the remedies should come into more intimate contact with the worms, and thus destroy them more easily, it is usual to clear out the intestine by a purgative some hours before the administration of the remedy, which is usually given on an empty stomach, or with a small quantity of milk. After some hours another purgative is given, in order to bring the worms away. As much mucus in the intestine forms a nidus for the worms, remedies which diminish it tend to prevent their occurrence. For this purpose preparations of iron and bitter tonics are useful.

CHAPTER XIV.

DRUGS ACTING ON TISSUE-CHANGE.

Tonics.

These are remedies which impart permanent strength to the body, or its parts. When an individual is loose and limp, and feels unfit for work, like a relaxed bowstring, tonics **restore** his **energy** and strength, and again fit him for work. As their action in this respect resembles the effect of tightening a bowstring, they have received the name of **tonics**, which is derived from *τόνος*, tension. The feeling of **debility** may depend on many different causes. It may be due to weakness of the muscles, or weakness of the nervous system. Again, the nerves and muscles may suffer because the circulation is languid and feeble, or because the blood which supplies them is deficient in oxygen, or in nutritive matter. These deficiencies again may depend on **deficient nutrition**, due to want of appetite, so that too little food is consumed, or to an improper or insufficient diet, or to imperfect digestion, so that the food is not assimilated. But weakness may be also induced by the **accumulation** of **waste-products** in the body, which interfere with the functional activity of the muscular and nervous systems; and these products may accumulate, because they are formed in excess in the tissues themselves by overwork, or in the intestinal canal from imperfect digestion; or because they may be allowed to pass too readily from the intestinal canal into the blood by deficient action of the liver.

Or their excretion may be defective from the kidneys being insufficiently active, or the bowels constipated.

The mode of action of tonics is so manifold that they have been divided into blood tonics or hæmatinics, vascular tonics, gastric tonics, intestinal tonics, and nervine tonics.

Uses.—In order to ascertain what form of tonic is required, it is necessary to determine carefully what part of the organism is in fault. In very many cases the imperfect functional activity in the body generally, which exhibits itself in languor and weakness, is due to accumulation of waste-products, and not to deficient nutriment. In such cases the plan of loading the stomach with food, and giving iron, wine, and beef-tea, simply

increases the mischief. If it is found, on examination of the urine, that the kidneys are not excreting a sufficient quantity of solids, and especially of urea, it is necessary to diminish the quantity of food, and especially of animal food, as all, or nearly all, the nitrogen taken into the body must be excreted by the kidneys.

In order that no unnecessary work be thrown on the kidneys, we must, as far as possible, prevent products of imperfect digestion from being absorbed from the intestinal canal, and therefore the state of the liver must be carefully attended to, and the bowels themselves carefully regulated.

In cases where the debility does not depend upon excessive waste-products in the blood and tissues, but upon defective oxidation due to deficiency of hæmoglobin, the patient must be treated by **hæmatinics** such as iron, cod-liver oil, and phosphate of lime. When the digestion is imperfect, gastric or **intestinal** tonics must be used as the case requires.

Where enfeeblement of the stomach appears to be present, as shown by loss of appetite, and such signs of imperfect digestion as flatulence or weight and pain after eating, **gastric** tonics are used. Should the muscular coat of the stomach be feeble or inactive, as shown by tendency to dilatation and splashing of the contents on movement, strychnine is especially indicated, and galvanism or systematic kneading may be also employed. Where the stomach is too debilitated to respond sufficiently to this form of treatment, as after long-continued gastric catarrh, or in old age, its work must be partly done for it, and then such **digestives** as hydrochloric acid and pepsin are useful. When the muscular movements of the intestine are sluggish, as indicated by constipation and by a tendency to distension of the bowel with gas, nux vomica and belladonna may be given; and when its mucous membrane appears to be relaxed and flabby, and secreting too profusely, the mineral acids, astringents, and metallic salts may be of much service. When the pulse is soft and feeble, and there is a tendency to vascular dilatation, either general or local, as shown by local congestion and œdema of the dependent parts, or by drowsiness in the upright position and sleeplessness in the recumbent posture, **vascular** tonics are serviceable. **Nerve** tonics are used where the nervous functions are imperfectly performed, as shown by dulness, loss of memory, incapacity for work, languor, paralysis, or tendency to spasm, as in chorea. As the functions of the nervous system depend very greatly upon the quality of the blood with which it is supplied, and on the rapidity of the circulation, the other tonics frequently require to be given in addition to nervine tonics.

Hæmatinics.

Blood-tonics, blood-restoratives, analeptic tonics.—These are generally remedies which improve the quality of the blood; but the name blood-tonics or hæmatinics is generally applied specially to such remedies as **increase** the quantity of red blood-corpuscles and **hæmoglobin** in the blood. The quality of the blood depends upon a number of conditions: upon the amount and nature of the food ingested, on the digestion, on the formation and excretion of the various products of tissue-change, and more especially on the formation and destruction of the red blood-corpuscles themselves.

The red **blood-corpuscles** are probably **formed** in the spleen, the medulla of bones, the liver, and possibly other parts of the body, from leucocytes which lose their nucleus, take up hæmaglobin, and alter their form to that of the red corpuscles.

The red corpuscles are probably **destroyed,** at least to a great extent, in the liver, and probably also in the spleen. The colouring matter of bile contains a quantity of iron, and appears to be formed from hæmoglobin.

An abnormal condition of the liver, by leading to excessive destruction of blood-corpuscles, may therefore be an important cause of anæmia. The corpuscles contain albuminous matters as well as hæmoglobin, and deficiency of albumen in the blood will lead to anæmia. Thus, in cases of Bright's disease, the loss of albumen through the kidneys tends to produce anæmia, and this must be combated by lessening the loss, if possible, as well as by supplying albumen.

The blood-corpuscles also contain fat, and deficiency of fatty food will tend to produce anæmia. Cod-liver oil, on the other hand, which is an easily assimilated form of fat, is a powerful hæmatinic. In anæmia there is a deficiency of iron in the blood, and chalybeate preparations are among the most powerful of all hæmatinics.

One well-marked disease due to imperfect nutrition is scurvy. In it there is not only a deficiency of red blood-corpuscles, but a tendency to extravasation. Its pathology is not definitely made out, and it has been supposed to be due to a deficiency of salts of potassium in the blood, but it is much more likely that it is due to increase in the chlorides, and especially chloride of sodium, either absolutely or relatively to the carbonates.

Excess of chloride of sodium causes the blood-corpuscles to pass out of the vessels (p. 63), and potassium salts alone, or beef-tea, which contains them, do not cure scurvy; but it is removed by fresh vegetables or by lime-juice.

Alteratives.

These are remedies which **improve** the **nutrition** of the body **without** exerting any very **perceptible action** on individual organs. The chief alteratives are:—

Arsenic.	Colchicum.
Mercury.	Guaiacum.
Iodine. Iodides.	Stillingia.
Cod-liver oil.	Sanguinaria.
Sarsaparilla.	Xanthoxylum.
Sulphur.	Mezereum.
Gold.	

Action.—Healthy nutrition depends (1) upon a proper supply of oxygen and nutriment to each tissue and organ in the body, (2) on the proper amount and kind of tissue-change in the various cells; (3) on the proper removal of waste.

The proper supply of oxygen and of nutriment to the body generally will depend upon the state of the respiratory and digestive organs; their proper supply to the tissues, as well as the removal of waste from them, will depend upon the circulation; and the removal of waste from the body generally will depend upon the bowels, skin, and kidneys.

The drugs which act upon the different organs just mentioned are considered under other headings, but the changes which take place in the tissues themselves appear to be effected by drugs which produce no marked corresponding changes in assimilation, circulation, or excretion. It is uncertain how they act: it is possible that they may alter in some way the action of enzymes in the body, but it is also possible that they act by replacing the normal constituents of the tissues and forming compounds which tend to break up in a different way from those which are ordinarily present.

Thus chloride of sodium and nitrogenous bodies such as albumen are amongst the most important constituents of the body; and we find that among the chief alteratives are substances which will replace chlorine, sodium, or nitrogen in many compounds. Thus we have iodine and iodides, and nitric or nitro-hydrochloric acids, which will displace or replace chlorine. We have chlorine itself, and chlorides which may alter the proportion of chlorides to other salts in the blood and tissues, and thus modify the solubility of various constituents of the tissues. We have salts of potassium and calcium, which may replace those of sodium; sulphur, and sulphides which may replace oxygen; phosphorus, hypophosphites, antimony and arsenic, which may replace nitrogen; mercury and its salts, which may replace calcium.

Besides these we have organic alteratives, regarding the action of which we can at present form no hypothesis unless

they influence the processes of digestion. Nitro-hydrochloric acids, taraxacum, and small doses of mercurials, probably act either by modifying the digestion of food in the duodenum and jejunum, or by modifying the changes which it undergoes in the liver after absorption.

The action of drugs upon tissue-change has usually been investigated by ascertaining the amount of urea excreted before, during, and after the administration of a drug. Most of the older experiments on this subject are of little or no value, as sufficient care was not taken to ensure that the amount of nitrogenous food consumed each day during the experiment was exactly the same. As all the nitrogen taken in the food reappears in the urine, any irregularity in the quantity introduced into the body will cause a corresponding irregularity in the quantity excreted. After this fact was ascertained, the plan adopted by some experimenters was to deprive an animal of food for several days, until the excretion of urea due to the gradual destruction of its nitrogenous tissues became nearly constant. The plan now adopted is to give to a dog or a man a quantity of food of a uniform quality and the amount of nitrogen in which is exactly known. The quantity given each day is exactly weighed. The same amount of nitrogen is thus introduced into the organism every day, and therefore any variations in the amount of nitrogen excreted must be due to changes in the organism itself.

Observations on the excretion of urea only give us a very partial and imperfect knowledge of the process of tissue-change, and they ought to be combined, as in the experiments of Pettenkofer and Voit, with observations on the amount of oxygen absorbed and of carbonic acid given off. Such experiments as these, although very valuable, are very laborious, and comparatively few have hitherto been made.[1]

From experiments made with those necessary precautions just described it has been found that free consumption of water increases tissue-change very considerably, as is shown by the increased excretion of urea.

Common salt, sulphate of sodium, phosphate of sodium, acetate of sodium, borax, nitrate of potassium, chloride of ammonium, carbonate of ammonium, and probably all salts which pass out in the urine carrying water with them, somewhat increase tissue-change and the amount of urea excreted. Fats and fatty acids apparently lessen the decomposition of albuminous tissues and the excretion of urea, but glycerine has no action of this sort. Alcohol in small or moderate doses lessens, in large doses increases, tissue-change. Benzoic acid, salicylic acid, and benzamide, all increase tissue-change. Contrary to what perhaps might have been expected, tea, coffee, and cocoa have no action whatever on the excretion of urea.[2] The experiments which seemed to show that they diminished it, appear to have been made without the necessary precautions. Morphine slightly diminishes the excretion of urea, but its action is much more marked on the consumption of oxygen and excretion of carbonic acid. These are

[1] A complete account of the whole subject is given by Voit in Hermann's *Handb. d. physiol.*, Band VI. Theil i. This contains also complete references to the literature.

[2] Voit, *op. cit.*

greatly increased in the stage of excitement, and greatly diminished in the stage of quiescence. It would appear that these changes are not due to the direct action of the morphine, but only to the alterations of muscular activity which follow its administration.

Quinine lessens tissue-change, iron appears to increase it, mercury also slightly increases it,[1] while iodine appears to have little influence upon the quantity of urea excreted. This fact is of itself, I think, sufficient to show that the mere estimation of the quantity of urea excreted before and after the administration of a drug is quite insufficient to give us any precise information regarding its action on tissue-metamorphosis.

Antimony, arsenic, and phosphorus have a special action on tissue-change, and powerfully affect the glandular, nervous, respiratory, and cutaneous systems. In large quantities they affect the liver very markedly, producing fatty degeneration; and this also occurs in other tissues.

This **fatty degeneration** is due to a twofold action:—1st, increased tissue-metamorphosis; and 2nd, diminished oxidation. In the normal condition albuminous tissues split up as indicated below:—

Albuminous tissues	split up into	Non-nitrogenous substances . .	e.g. Fat, &c.	converted in health into	Carbonic acid, excreted by lungs.
		Nitrogenous substances	e.g. Leucin, Tyrosin, &c.		Urea, excreted by kidneys.

In poisoning by antimony, arsenic, and phosphorus, the nitrogenous products of tissue-waste appear in much larger quantity in the urine than normally, owing to the increased decomposition which is going on. They may appear in the urine in the form of an excessive quantity of urea, as in cases of phosphorus-poisoning in the dog, but in man they may appear in the form of leucin and tyrosin. Owing to the diminished oxidation the non-nitrogenous substances remain in the body as fat, instead of being oxidised and passing out of the body as carbonic acid.

The exact nature of their effect on the nervous system has not been made out. Their action on the skin and epithelial cells of the lungs seems to be that of causing fatty degeneration.

Fatty degeneration of the liver occurs also in poisoning by salts of silver.

Mercury has a peculiar power of breaking up newly deposited fibrin and of causing disorganisation of syphilitic deposits. Iodine, iodides, and probably also chlorides, appear to act on the lymphatic system and promote absorption: their action is specially well-marked in cases of glandular enlargement.

Uses.—In general malnutrition without definite symptoms, mercurials, taraxacum, and nitro-hydrochloric acid are used and

[1] Boeck, quoted by Voit, *op. cit.*

are especially indicated where the liver is suspected to be in fault, as where there are symptoms of biliousness, and also where oxalates and urates are found abundantly in the urine.

In gout, salts of potassium and colchicum are used. Phosphorus and arsenic are employed in nervous debility: and they, as well as antimony, are serviceable in neuralgia, chorea, and other nervous diseases.

In diseases of the skin, arsenic is chiefly employed.

In diseases of the respiratory organs, antimony is very serviceable when the attack is acute; and arsenic is most valuable in some chronic conditions, especially in chronic consolidation, where it probably acts by producing fatty degeneration and softening of the effusion, so that it is either absorbed or expectorated.

Mercury is employed specially to break up deposits of lymph and to prevent adhesions, as in iritis and pericarditis; and is also used and is most serviceable in the treatment of syphilis. It is most generally employed in the secondary stage of this disease: in the third stage it is either given along with, or entirely replaced by the use of, iodides.

Antipyretics, Febrifuges.

These are remedies which **reduce** the **temperature** of the body in fever. They act much more powerfully when the temperature is abnormally high than when it is normal.

The constant temperature of warm-blooded animals depends upon the maintenance of a proper balance between the amount of heat generated in the body, chiefly by oxidation, and the amount given off to the surrounding medium—air or water. The heat is chiefly generated in the muscles and glands. It is chiefly given off by the skin, although some is also lost by the lungs, etc.

A little heat, but not much, may be given off by radiation alone. The power of dry air to take up heat is very slight, and so the skin is not much cooled, and very little sensation of cold is felt at temperatures much below 0° if the air is both still and dry. If the air be moist its capacity for heat is much greater, and the loss of heat from the skin being much more rapid, a person may actually feel the weather colder at 4° F. than at −40° F., the air being still in both cases. If air, either dry or moist, is in motion, so that fresh portions of it come successively into contact with the skin, the loss of heat is much more rapid, and a little wind will render even dry air unbearably cold at a temperature which would be quite supportable if the air were still.

Loss of heat occurs more readily in small animals than in large. This is represented diagrammatically in Fig. 144.

It is to be observed that during sleep the action of the vaso-motor centre is less, the vessels of the surface dilate, and loss of

heat, with danger of consequent chill, takes place more rapidly. For the effects of local chill to the surface, the results of Rossbach's experiments may be consulted (p. 251).

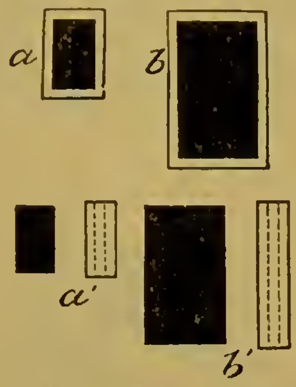

FIG. 144.—Diagram to show that loss of heat occurs more readily in small animals than in large. The unshaded part in *a* and *b* represents the surface through which heat is lost; the black part shows the heat-producing part of the body. These are shown separately in *a′* and *b′*, from which it is evident that in the small animal the heat-producing area is about the same size as, while in the large animal it is double the size, of the heat-dispersing area.

But heat may be generated in muscles and glands apart from the circulation in them, and Sachs and Aronsohn have shown that a centre regulating the production of heat is situated in the

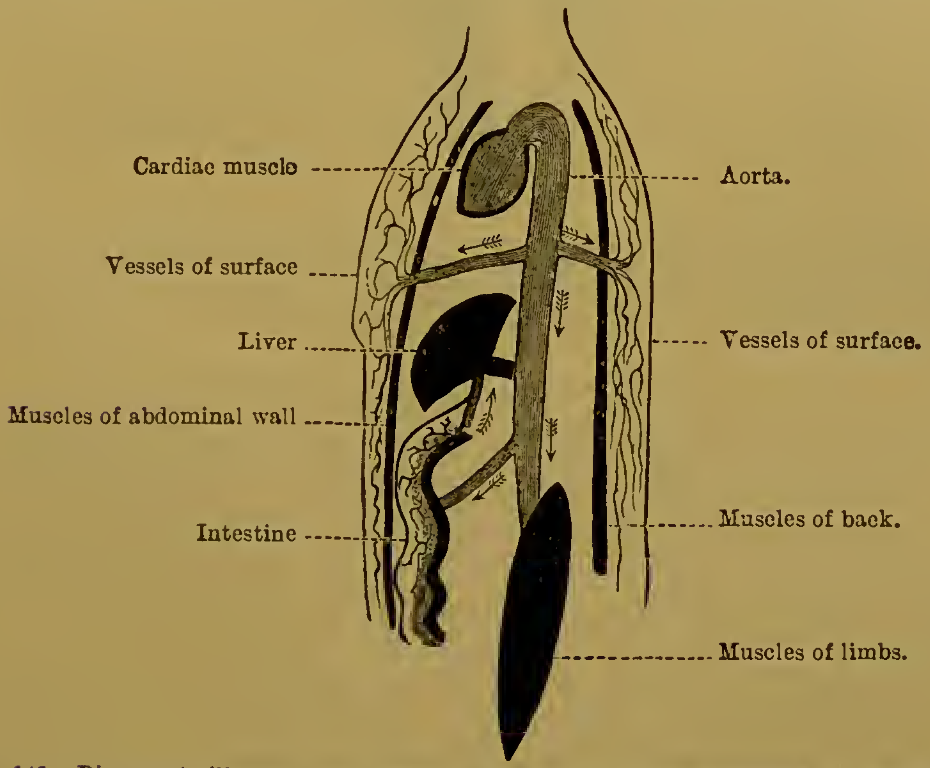

FIG. 145.—Diagram to illustrate the action of alterations in the circulation of the surface of the body and the internal organs and muscles upon temperature. In this figure the superficial vessels are represented as contracted, and there is therefore not only less loss of heat, but the blood being driven to the internal organs and muscles, the circulation in them is increased and the production of heat augmented. The parts where heat is produced are the dark, the darkness being in proportion to the greater production. The parts where heat is retained without much being formed, e.g. the blood, are moderately shaded. Those where heat is lost are left white. In the intestine heat is both formed and lost (p. 418), and so the intestines are partly dark and partly light.

neighbourhood of the corpora striata.[1] It is probable that the temperature may be affected by drugs acting on the nervous

[1] *Deutsche med. Wochenschr.*, December 1884.

system apart from the circulation and also by drugs which affect the tissues themselves (p. 58 *et seq.*).[1]

The circulation exercises a very important influence upon (1) the amount of **heat lost** from the surface and (2) the amount of **heat produced** in the internal organs and muscles. This is represented diagrammatically in Figs. 145 and 146.

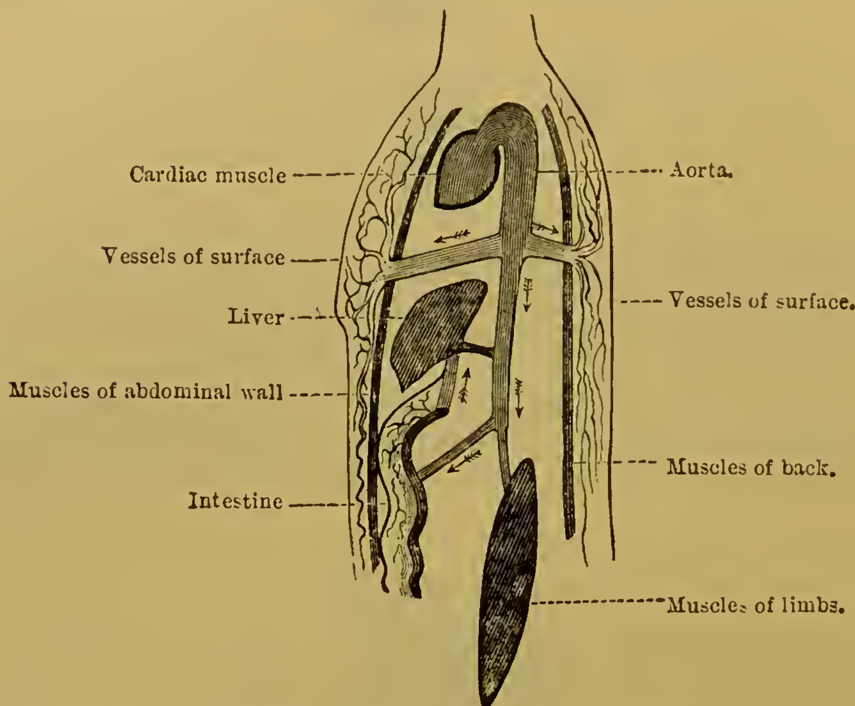

FIG. 146.—Diagram to illustrate the action of alterations in the circulation of the surface of the body and the internal organs and muscles upon the temperature. In the diagram the cutaneous vessels are represented as dilated, and thus not only is more heat lost from the surface, but, blood being withdrawn from the internal organs and muscles, the circulation in them is lessened and less heat produced.

The vessels of the skin form a cooling apparatus (p. 440), while heat is generated in the muscles, voluntary and involuntary, and in glands, e.g. the intestine and liver. The intestine is, however, only protected by the thin abdominal walls from the cooling action of the external air, and so it may act either in cooling or warming the body, according to circumstances.

When the vessels of the surface are dilated, the blood not only courses freely through them and becomes cooled, but, being withdrawn from the muscles and glands, there is less heat produced. The reverse is the case when the cutaneous vessels are contracted. The condition of the vessels depends on the action of the vaso-motor centre, and drugs acting upon it may greatly modify the temperature.

Antipyretics may be divided into two great classes: those which **lessen** the **production** of heat, and those which **increase** the **loss** of heat; and these again may be subdivided as shown in the following table:—

[1] Umbach, *Archiv f. exp. Path. u. Pharm.* 1886, xxi.

- **Anti-pyretics**
  - Lessen production of heat
    - Acting on tissue-change
      - Quinine.
      - Cinchonine.
      - Quinidine.
      - Cinchonidine.
      - Berberin.
      - Benzoic acid.
      - Carbolic acid.
      - Picric acid.
      - Salicylic acid.
      - Salicylate of sodium.
      - " quinine.
      - " methyl. (oil of winter-green).
      - Salicin.
      - Kairin.
      - Camphor.
      - Eucalyptol.
      - Thymol.
      - Other essential oils.
      - Alcohol.
    - Acting on the circulation
      - Generally
        - Antimony salts.
        - Aconite.
        - Digitalis.
        - Veratrine.
        - Colchicum.
        - Thallin.
      - Locally
        - Wet cupping.
        - Leeches.
        - Dry cupping.
        - Blisters.
        - Poultices.
  - Increase loss of heat
    - By dilating the cutaneous vessels, and increasing radiation
      - Alcohol.
      - Nitrous ether.
      - Antipyrin,[1] thallin.
    - By increasing the loss of heat due to evaporation of perspiration — Sudorifics
      - Antimonial preparations.
      - Opium and ipecacuanha.
      - Nitrous ether.
    - By abstracting heat from the body
      - Cold bath.
      - Cold affusion.
      - Cold sponging.
      - Wet pack.
      - Ice to the surface.
      - Ice-bags to the neck.
      - Cold drinks.
      - Cold enemata.
  - Mode of action uncertain
    - Purgatives.
    - Venesection.

The mode of action of those which affect the blood and tissues themselves has already been considered tolerably fully under the head of 'Oxidation of Protoplasm' (p. 67). They appear simply to diminish the temperature by lessening oxidation. The mode of action of antipyretics which produce their effect through the circulation, has not been investigated in detail with satisfactory exactitude, but it is supposed that by lessening the rapidity of the circulation through those parts of the body in which the increased tissue-change is taking place, the temperature is reduced.

Blisters will have this effect locally by causing contraction of the vessels in the inflamed part, as already described under the head of Counter-Irritants (p. 343).

Antipyretics, which increase the loss of heat, may do so (1) by causing greater dilatation of the vessels of the skin, and thus

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[1] Bettelheim, 'Ueber das Antipyrin,' *Wien. med. Jahrbücher*, 1885.

allowing a quicker radiation of heat from the body; (2) by augmenting the secretion of **sweat**: and thus carrying off heat by means of evaporation (see Diaphoretics, p. 440); or (3) they may actually **remove warmth** from the body, as cold baths, cold affusion, cold sponging, wet packing, cold enemata, or ice to the surface.

Uses.—Antipyretics are used to **lower** the **temperature** when it has risen above the normal, whatever be the cause. A high temperature may be produced simply by prolonged exposure to heat. This exposure and the rise in temperature it occasions, seems to induce increased tissue-change, and this increase of the tissue-change will keep up a febrile temperature, even after the external temperature has fallen. Such thermal fever is found in warm climates, and in it quinine injected subcutaneously seems to be very efficient.

A high temperature may also occur from specific fevers, as typhus, typhoid, scarlet fever, measles, and acute rheumatism. The most rapid and powerful antipyretic in such cases is the application of cold by bathing, or sponging; and probably next in efficiency come large doses of quinine or salicylate of sodium. In typhoid fever, salicylate of sodium does not seem to act so rapidly as it does in acute rheumatism.

Venesection, though formerly the antipyretic which was chiefly relied upon, has now fallen to a great extent out of use—probably from its having been very much abused.

In persons suffering from acute inflammation of the lungs or bronchi, where the amount of lung-tissue which remains sound is insufficient to aërate the whole mass of blood, and the patient is becoming livid, small bleedings are serviceable; they not only relieve the breathing, but lessen delirium which may be present.

Venesection lowers the temperature for a short time, but it soon rises again in many cases, so that bleeding alone is by no means a powerful antipyretic,[1] unless the quantity of blood abstracted be so great as probably to injure the patient seriously; yet in combination with other antipyretics it may sometimes be of very great service.

Local bleeding by **leeches** or by **wet cupping** sometimes gives very great relief, lessening both local inflammation and the general symptomatic fever consequent upon it, in pneumonia, pleurisy, pericarditis, peritonitis, &c. In such cases blisters may be used to diminish the local inflammation, and thus aid the action of other antipyretics.

Vascular antipyretics, such as aconite and digitalis, also seem to be of more service in symptomatic fever than they are in specific fevers.

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[1] Wunderlich's *Medical Thermometry*, pp. 118, 134, 378, New Sydenham Society's edition.

Purgatives take an intermediate place between antipyretics which lessen the production of heat by acting on the tissues, and those which act on the circulation. They diminish the force of the circulation, and may in this way lessen the production of heat. But it is not impossible also, although this is a point on which we have not sufficient information, that they may do so by removing from the body substances whose effect when present in the circulation or tissues would be to maintain the high temperature.

Amongst antipyretics which increase the loss of heat we have: first, alcohol, which is included also in the former list of those which lessen the production of heat, for it appears to act in both ways, both diminishing oxidation and also increasing the loss of heat. It does this by dilating the vessels of the skin and allowing free radiation from the surface, and also by the cooling effect of evaporation of the sweat, although its action as a sudorific is not very marked. Antipyrin seems to act in a similar manner.

We have also the whole class of **sudorifics** (p. 440). One of the most useful of these in checking a febrile condition just at its outset is a dose of compound ipecacuanha powder, or Dover's powder, which has now, to a great extent, taken the place of the older remedy having a somewhat similar action, viz. antimonial powder, or James's powder.

Another mixture in great favour is acetate of ammonium and spirit of nitrous ether. The most powerful, however, of all remedies which increase the loss of heat is the application of **cold** water or ice. The mode of applying these is discussed at page 464.

CHAPTER XV.

ACTION OF DRUGS ON EXCRETION.

ACTION OF DRUGS ON THE KIDNEYS.

The kidney has a twofold office. It has (1) to regulate the amount of water in the body under various conditions; (2) to remove the products of tissue-waste. These products must be removed in a state of solution from the part of the kidney where they are excreted, and yet sometimes provision must be made for the water, by which they are washed out, being retained in the body. The urine in mammals and amphibia is liquid; in birds and reptiles it is semi-fluid or solid, yet the solid constituents are removed in solution from the urinary tubules, and the water in which they are dissolved is afterwards absorbed. We may say then that the kidney has not only a twofold, but a **threefold action**:—1st, the **excretion** of **waste**-products; 2ndly, a provision for the **removal** of excessive **water**; and 3rdly, an arrangement for the **retention** of **water** in the body, by its re-absorption after it has washed out the waste-products. On looking at the kidney we find three structures which seem to be connected with these three functions, viz.: (1) **convoluted tubules** with epithelial cells, which in all probability are the chief structures for excreting waste-products; (2) the **Malpighian corpuscles** for excreting water along with some solids, and (3) usually one or more **constrictions** in the tubule which may serve the purpose of preventing too rapid exit of the water, and thus allow time for its re-absorption in cases where its retention is desirable, as for example on a hot day and when the supply of drinking-water is very limited.

The process of **secretion** in the kidney was regarded by Bowman as consisting of the filtration of water from the vessels of the glomeruli into the tubules, and the excretion of waste-products by the epithelium lining the tubules. Ludwig, however, came to look upon it rather as a process of filtration and re-absorption; a dilute solution of urea and salt being, according to him, poured out from the Malpighian corpuscles and gradually concentrated by the absorption of water in its passage along the tubules. This theory had so many facts in its favour that it was

for a good while exclusively adopted, but latterly Heidenhain, in an admirable series of experiments, has shown that such substances as indigo are certainly excreted by the epithelium of the tubules. At the same time Hüfner has shown, by a comparison of the structure of the kidney in fishes, frogs, tortoises, birds, and mammals, that the form of the tubules closely agrees with that required for the re-absorption of water in each case. Fishes have a low blood-pressure, and so the resistance in the kidney requires to be small in order to allow of the secretion of urine. Living as they do in water, they do not require any apparatus for its retention in the body. In them therefore

FIG. 147.—Diagram showing the form of the urinary tubules in different classes of animals, after Hüfner. 1. Fish. 2. Frog. 3. Tortoise. 4. Bird. 5. Mammal. The letters have the same signification in each. *a*. Capsule of the glomerulus. *b*. Convoluted tubule. *c*. Loop. *d*. Collecting tubule. *u* in 2 indicates the transverse section of the ureter.

the tubule is short and wide, and destitute of any constriction which would retard the outflow of the fluid. In frogs there must be ample provision for the retention of water in the body, as evaporation takes place freely from their skin. In them we find, as we might expect, that the tubule, and especially the contracted part of it, is very long. In tortoises no evaporation from the skin can take place, and in them the contracted part of the tubule is short. This renders it probable that, while the ideas advanced by Bowman and supported by Heidenhain are in the main true, the re-absorption of water on which Ludwig lays so much stress is also an important factor in the secretion of urine under different circumstances.

But it is not only rendered probable by the facts of compara-

tive anatomy; it appears to be proved by direct experiment. Ribbert[1] has extirpated the medullary substance of the kidney in the rabbit while leaving the cortical substance. He has thus succeeded in collecting the urine as it is excreted by the Malpighian corpuscles before it has passed through Henle's loops, and has found that the urine secreted by the cortical substance alone is much more watery than that which is secreted by the entire kidney—a fact which appears conclusively to prove that water is actually re-absorbed, and the urine rendered more concentrated, during its passage through the tubules of the medullary substance.

In the frog and triton the arrangement of the kidney is such as to allow of a much more complete investigation of the different factors in secretion, than in mammals, because in amphibia, the glomeruli which separate the water and the tubules which excrete the solids, receive their blood-supply to a great extent independently. The glomeruli are supplied by branches of the renal artery. The tubules are supplied by a vein which proceeds from the posterior extremities and, entering the kidney, breaks up into a capillary plexus bearing a somewhat similar relation to the renal tubules as that which the portal vein does to the lobules of the liver. It is therefore called the portal vein of the kidney.

The arterial circulation in the glomeruli and the venous portal circulation round the tubules are not entirely distinct, for the efferent arteries of the glomeruli unite with the portal capillaries, and, moreover, arterial twigs also pass directly from the renal artery into the capillary venous plexus (*vide* Fig. 148). The two systems are so far distinct that Nussbaum has been able to ascertain with considerable exactitude the part played by each in secretion, although Adami[2] has shown that the communication is freer than Nussbaum supposed. By ligaturing the renal artery Nussbaum destroyed the functional activity of the glomeruli, and by ligaturing the portal vein of the kidney he destroyed that of the tubules. By injecting a substance into the circulation after ligature either of the artery or the vein; and observing whether it is excreted or not, he determines whether it is excreted by the glomeruli or by the tubules. In this way he finds that sugar, peptones, and albumen pass out through the glomeruli exclusively, for they are not excreted when the renal arteries are tied. Albumen, however, only passes out through the glomeruli when an abnormal change has already occurred in the vascular wall; as, for example, after the circulation has been arrested for a while by ligature of the renal artery. Indigo-carmine, when injected after ligature of the renal arteries, passes into the epithelium of the tubules, but it does not give rise to any secretion of water, so that the bladder is found empty.

[1] Ribbert, *Virchow's Archiv*, July 1883, p. 189.
[2] Adami, *Journ. of Phys.*, vol. vi. 1885.

Urea, on the contrary, is not only excreted by the tubules after ligature of the renal artery, but carries with it, in the process of secretion, from the venous plexus, a considerable quantity of water, so that the bladder becomes partially filled.

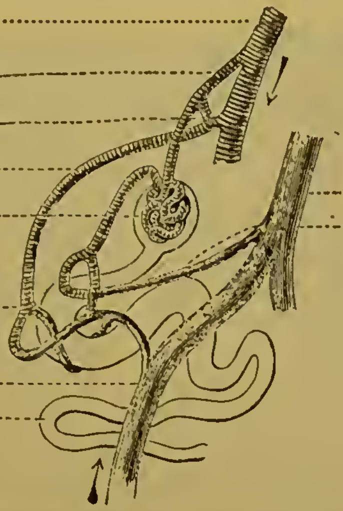

FIG. 148.—Diagram of the circulation in the kidney of the newt. Modified from Nussbaum.

The excretion of water, therefore, takes place in a double manner: it passes out through the glomeruli when the renal arteries are free, and it passes out from the venous plexus along with urea, even although the renal arteries are tied.

FIG. 149.—Diagrammatic sketch of the blood-vessels in a mammalian kidney. *O* is an artery ascending into the cortical substance of the kidney; *p* is a branch from it which divides into two branches, *q* and *P*. *q* breaks up at once into a number of twigs. *P* is the afferent artery to a glomerulus, *S*, of the lowest row. *t* is the efferent vessel of the glomerulus. It divides into two branches, one of which, *u*, ascends towards the cortex, whilst the other, *v*, descends towards the medulla. (From Schweigger-Seidel, *Die Nieren*, Halle; 1865.)

In the kidneys of the higher animals (Fig. 149) and of man the glomeruli and the tubules do not receive blood from two entirely different sources; but there is an arrangement somewhat similar, for the plexus surrounding the tubules does not receive blood only from the efferent vessels of the Malpighian corpuscles, but gets it also directly from the renal arteries. There are three channels by which the blood may pass from the renal arteries into the venous plexus without going through the glomeruli. The first is the inosculation which takes place between the terminal twigs of the renal artery and the venous plexus on the

surface of the kidney directly under the capsule.[1] The second channel is formed by small branches given off directly by the interlobular arteries or by the afferent arteries before they reach the glomeruli. The former of these may be regarded as corre-

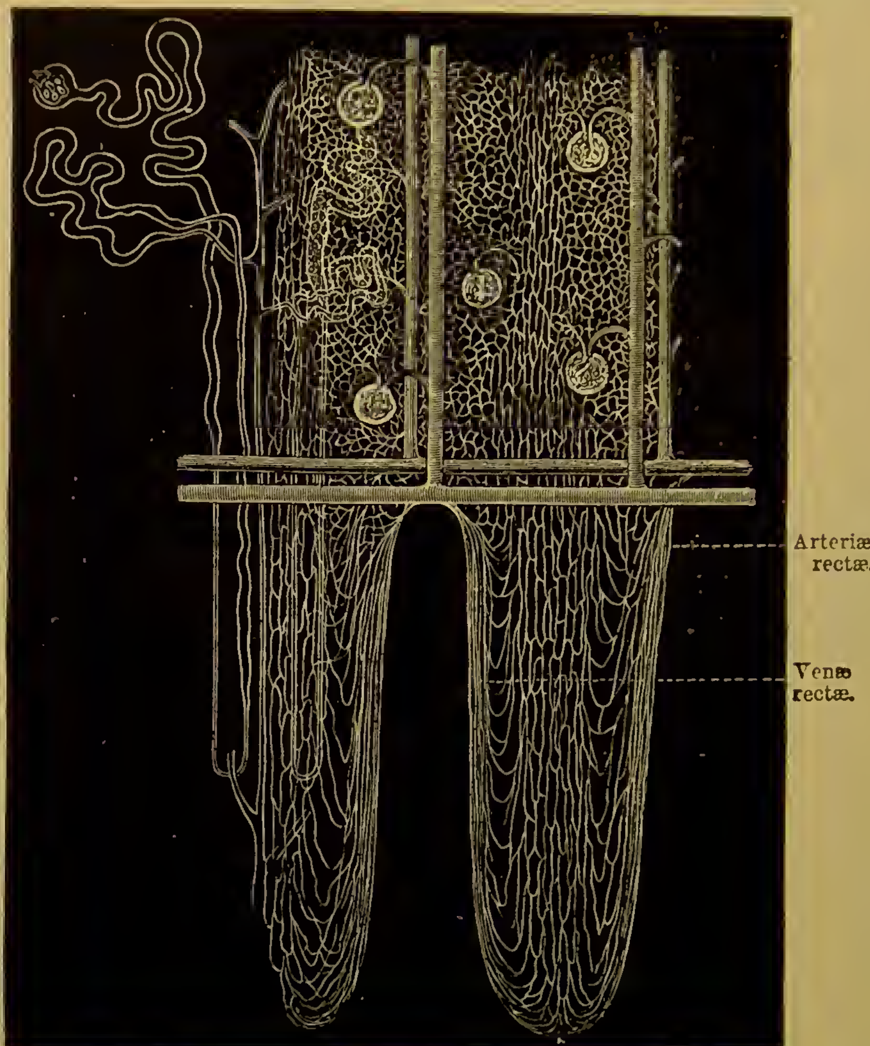

FIG. 150.—Diagram of the tubules and vascular supply of the kidney. On the left is a tubule alone; in the middle is a tubule along with the blood-vessels; on the right are blood-vessels only.

sponding to the artery which passes directly to the plexus in the newt, and the latter to the branch connecting it with the afferent artery (Fig. 148). These arterial twigs are found not only near the surface of the kidney, but also in the deeper layers of the cortical substance.[2] The third and most important channel is afforded by the arteriæ rectæ, which spring from the branches of the renal artery at the boundary between the cortical and medullary substance and pass into the medulla, where they form a plexus with elongated meshes surrounding Henle's loops and the collecting tubules. Near their origin the arteriæ rectæ

[1] Ludwig, *Handwörterbuch d. Physiol.*, v. R. Wagner, Bd. 2.

[2] Schweigger-Seidel, *Die Nieren*, p. 67; Heidenhain, Hermann's *Handbuch d. Physiologie*, vol. v., Th. 1, p. 293.

inosculate with the venous plexus surrounding the convoluted tubules (Fig. 150).

Through these three channels it is possible for blood to reach the secreting structures of the kidney and there get rid of urea, salts, &c., without losing water by its passage through the glomeruli. On the other hand, if these vessels contract, while the size of the renal artery and the pressure of the blood within it remain unaltered, more blood will be forced into the Malpighian corpuscles, and thus the quantity of water excreted will be increased. At the same time the contraction of the arteriæ rectæ will probably diminish absorption from the tubules, and thus the quantity of water excreted will be increased in a twofold manner.

Circumstances Modifying the Secretion of Urine.—The experiments of Ludwig and his pupils have shown that the amount of urine secreted depends very closely upon the pressure of blood in the Malpighian corpuscles, or, to put it more exactly, on the **difference** of **pressure** between the blood in these corpuscles and the pressure within the tubules. For if the ureter be tied so that the pressure of urine in the tubules is increased, the secretion is greatly diminished, and even arrested, even though the pressure of blood in the renal artery be high.

A somewhat similar effect to that of ligature of the ureter is produced by ligature of the renal vein, for the blood accumulating in the venous plexus surrounding the tubules compresses them so as to prevent the flow of urine through them. A similar condition may occur from cardiac or pulmonary disease obstructing the venous circulation.

But unless under exceptional circumstances which alter the pressure within the tubules, such as compression of the tubules by congestion of the venous plexus, as in cardiac disease, impaction of a calculus in the ureter, or pressure on the ureters by dropsical accumulations or tumours, the rapidity of the **secretion** of urine depends on two factors: (1) **arterial pressure** in the glomeruli; and (2) the **composition** of the **blood**.

The **pressure** of blood in the glomeruli may be **raised**:

(1) By increase of the arterial tension generally.

(2) By increased tension locally.

Such a **general** increase may be brought about by greater action of the heart, or by contraction of the blood-vessels in other vascular areas, such as the intestines, muscles or skin, by nervous stimulation, exposure to cold, or the action of drugs.

The pressure may be increased **locally** by dilatation of the renal arteries, e.g. from section of the vaso-motor nerves, or possibly stimulation of vaso-dilating nerves.

In addition to such increase of pressure in the glomeruli by increase of blood-supply to them, we must not, however, forget the possibility of increased pressure in them by contraction of the efferent vessels leading from them, as well as of those

arterial twigs (arteriæ rectæ) which pass directly to the venous plexus surrounding the tubules, and which form no inconsiderable part of the vascular supply of the kidney.

Alterations in the size of the renal vessels were formerly ascertained simply by exposing the kidney and observing its colour, contraction of the arteries being associated with paleness, and dilatation with redness of the organ. A much more exact method has been introduced by Roy, who encloses the kidney in a capsule filled with oil and connected with a registering apparatus. When the vessels dilate, the kidney increases in size, and diminishes when they contract, so that the alterations can be readily recorded on the same revolving cylinder on which the general blood-pressure is registered by the manometer.

The **pressure** of blood in the glomeruli may be **diminished** generally:

(1) By failure of the heart's action; or

(2) By dilatation of the vessels of large areas, as the intestines, muscles, or skin.

The pressure of blood in the glomeruli may be **diminished locally** by contraction of the renal arteries, or of the afferent branches to the glomeruli.

The heart's action may fail from many causes, which have already been discussed more particularly.

Dilatation of the vessels in the skin, intestines, &c., may be caused by exposure to warmth, by the action of drugs, or by paralysis due to nervous injury.

Section of the splanchnics or of the spinal cord causes paralysis of the renal arteries, and ought, therefore, to increase the secretion of urine. This does occur, though not invariably, when the splanchnics are divided; but section of the spinal cord, by paralysing the intestinal and other vessels, lowers the blood-pressure so much that the supply of blood to the kidney is not only much below the normal, but is so small that the secretion of urine is generally almost completely arrested.

The **nerves** of the kidney consist of a number of small branches running along the renal artery and containing a number of ganglia. When these nerves are **cut** the vessels of the kidney dilate; when they are stimulated the vessels contract. A number of those fibres pass to the kidney from the spinal cord through the **splanchnics**, so that when the splanchnics are cut the vessels of the kidney usually dilate, and when they are irritated they contract.

The whole of the nerves, however, do not pass through the splanchnics, for stimulation of a sensory nerve, of the medulla oblongata, or of the spinal cord in the neck, will cause contraction of the renal vessels after both splanchnics have been cut, and section of the splanchnics does not always cause the renal vessels to dilate.

The **nervous centre** for the renal arteries is probably, like the chief vaso-motor centre for the body generally, in the medulla oblongata; but in all probability there are also subsidiary centres in the spinal cord and in the solar and mesenteric plexuses.

The reason for supposing these latter centres to exist is, that stimulation of the peripheral end of the splanchnic, divided at its passage through the diaphragm, causes contraction of both kidneys, and the vessels of the kidney of the side opposite to the stimulated nerve commence to contract later than those on the same side. A delay like this in the action of the stimulus indicates that it has not acted directly, but through the medium of ganglia.

When the splanchnics are divided the vessels of the kidney sometimes dilate and the kidney increases in size; a profuse secretion of urine may take place, which quickly increases to a maximum and remains for a considerable time. This, however, is not a constant effect, and not unfrequently the vessels do not dilate, and the kidney, instead of increasing, diminishes in size. This is what to a certain extent might be expected, inasmuch as a section of the splanchnics causes dilatation of the intestinal vessels and lowers the blood-pressure, and thus diminishes the supply of blood to the kidney.

When a puncture is made in the medulla oblongata in the floor of the fourth ventricle, profuse secretion also occurs, but this differs from that caused by section of the splanchnics, in being preceded by a slight diminution, by rising rapidly to a maximum and then rapidly falling. These characters seem to show that it is due to irritation of some vaso-dilating mechanism,[1] rather than to any paralysis.

Stimulation of the vaso-motor centre in the medulla oblongata by venous blood, or by drugs such as strychnine or digitalis, has a twofold action on the kidney, for it tends to cause contraction not only in the vessels of the kidney, but in those of other parts of the body. The effect upon the kidney is thus a complicated one, for the contraction of the intestinal and other vessels by raising the blood-pressure tends to drive blood into the kidneys, at the same time that the contraction of the renal arteries tends to keep it out. When the renal nerves are cut, the renal vessels no longer oppose the entrance of blood, and therefore the renal vessels dilate very greatly when the vaso-motor centre is stimulated; but when the renal nerves are intact the result is a varying one, for sometimes contraction of the renal vessels may be so great as to prevent the entrance of blood into the kidney, however high the general blood-pressure may rise; at other times the general high blood-pressure may be able to dilate the renal arteries in spite of any resistance they may offer. These different conditions may occur subsequently to one another; and this stimulation of the vaso-motor centre may cause contrac-

[1] Heidenhain, Hermann's *Handbuch der Physiologie*, vol. v. Th. 1, p. 366.

tion of the renal vessels, succeeded by dilatation, or *vice versâ*. Thus Mr. Power and I found that on injecting digitalis into the circulation of a dog, the blood-pressure rose, but the secretion of urine was either greatly diminished or ceased altogether. Here it is evident that the renal vessels had contracted so much as to prevent the circulation through the kidney, notwithstanding the

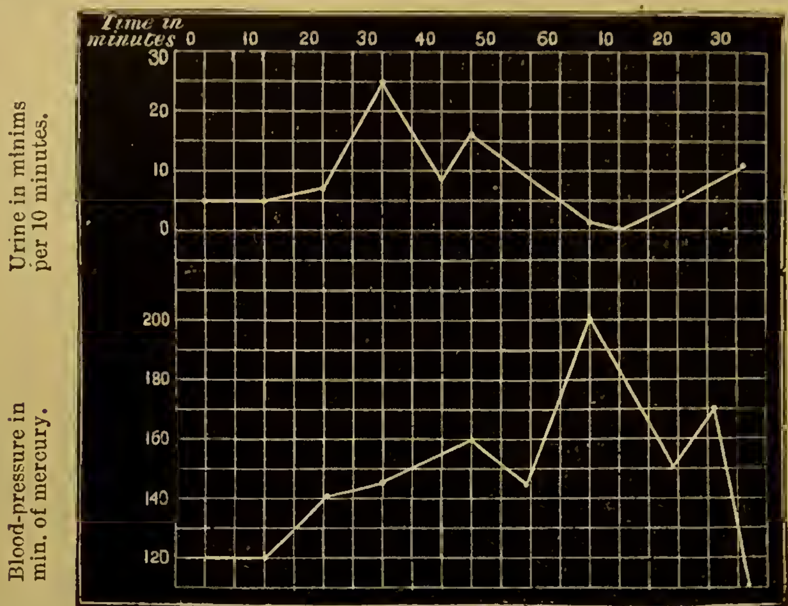

FIG. 151.—Curves showing the effect of erythrophlœum upon the blood-pressure and secretion of urine. From *Phil. Trans.*, vol. clxvii.

rise which had taken place in the blood-pressure. After a while the blood-pressure began to fall, and then the secretion of urine rose much above its normal, showing that the general blood-pressure was then able again to drive the blood into the kidneys.[1]

Similar observations were made by Mr. Pye and myself with regard to erythrophlœum; and the accompanying curves (Fig. 151) show well the result upon the urine of the mutual action of the rise in blood-pressure and the contraction of the renal arteries upon the secretion of urine. It will be noticed that at first the blood-pressure rises more quickly than the secretion of urine, the circulation through the kidney appearing to be opposed by the renal arteries. This opposition is then overcome, and the secretion of the urine rises more quickly than the general blood-pressure. The renal vessels again appear to contract, so that the urine diminishes while the blood-pressure rises still further. We have then oscillations due first to one factor and then to the other being predominant; and then, when the blood-pressure rises to its maximum, we find that the urine is at its minimum, the secretion of urine again rising as the blood-pressure falls.

A good deal of discussion has arisen regarding the mode of action of digitalis, and it has been stated by many to act as a diuretic only in cases of heart disease, and to have no diuretic

[1] *Royal Society's Proceedings*, No. 153, 1874.

action in health. In my own experiments, however, I found that it acted as a very marked diureticeven in health, and the explanation of this discrepancy may possibly be that in my own case the blood-pressure was low, whereas in the others it was probably much higher; but I am uncertain regarding the true explanation, though I am certain of the fact.

By causing increased secretion of water through the kidneys diuretics may increase the concentration of the blood and thus produce thirst, or cause absorption of water from the intercellular tissue or serous cavities in dropsies. In my own experiments on digitalis I weighed all my food and measured all my drink for nearly six months, taking exactly the same quantity every day. After producing profuse diuresis by a large dose of digitaline (sixty milligrammes in two days), such thirst ensued that I was forced to take a quantity of water to allay it.[1]

Mode of Action of Diuretics.—From what has already been said, it is evident that diuretics may act in several ways. They may act:

A, on the **circulation** in the kidney, raising the pressure

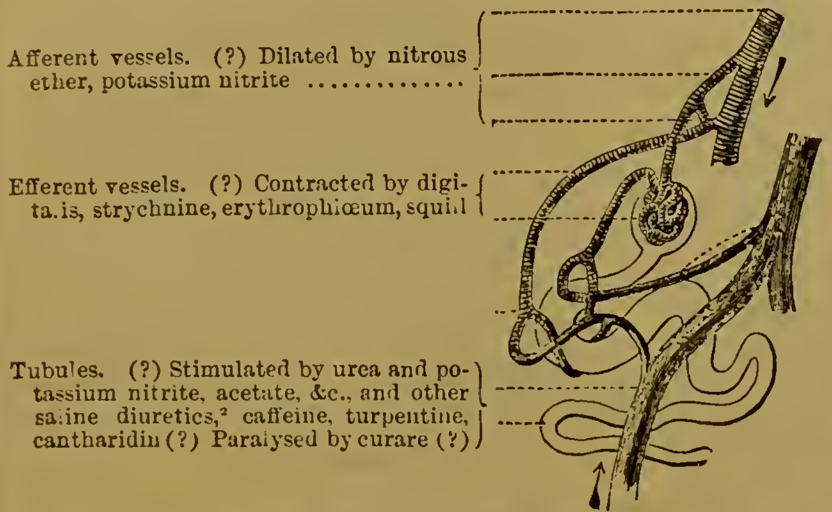

FIG. 152.—Diagram to show the parts of the secreting apparatus of the kidney which are probably affected by different diuretics.

in the glomeruli—(1) locally, (*a*) by contracting the efferent vessels, or the arterial twigs which pass directly to the capillary plexus; (*b*) by causing dilatation of the renal arteries, and thus increasing the supply of blood to the kidney. This they may do also in more ways than one, for they may either paralyse the vaso-motor nerves of the kidney, or act on vaso-dilating mechanisms. (2) they may raise the blood-pressure generally by causing the contraction of vessels in other parts of the body.

B. Other diuretics may act on the **secreting cells** of the tubules, and may increase both the amount of water and the amount of solids excreted by them.

[1] The experiments were made in 1855, and published in part in my thesis on *Digitalis, with some Observations on Urine*. London: Churchill & Co., 1868.

[2] Munk, *Central. f. d. med. Wiss.*, No. 27, 1886.

Calomel in continued doses acts as a powerful diuretic,[1] possibly by increasing the amount of urea in the blood, and thus increasing the amount of urine.[2]

Diuretics have already been classified as stimulating and sedative; and the sedative class agrees very closely with the one which we have just indicated as acting on the kidney through the circulation.

From what has been said of the action of diuretics it is evident that we may hope to do much more by combining them than by using them singly. Thus we see that digitalis instead of acting as a diuretic may completely arrest the renal circulation and stop the secretion altogether. If, however, we can combine it with something which will produce dilatation of the renal vessels, while the general blood-pressure remains high, we shall greatly increase the circulation through the kidney, and obtain the desired result. Experiments in regard to this were made by Grützner with nitrite of sodium. He found that this substance increased the secretion of urine when the blood-pressure was reduced to a minimum by curare; and he found that it also had this effect when the blood-pressure was raised by imperfect respiration. When the vaso-motor centre was greatly stimulated, however, by allowing the blood to become very venous, the nitrite of sodium no longer produced any increase of secretion.

Caffeine, again, has an action on the kidney similar to that of physostigmine on the salivary glands (p. 358). Thus, by affecting the vaso-motor centre, it not only produces contraction of the vessels generally, including those of the kidney,[3] but stimulates the secreting cells.[4] The contraction of the vessels may counteract this stimulating action, so that no urine is secreted as in the case of digitalis (p. 430), but when the renal nerves are divided a copious secretion of urine takes place.

Diuretics.

Refrigerant Diuretics.

Water in large quantities.
Carbonic acid (aërated waters).
Sodium salts, e.g. common salt.

Potassium salts, especially the
Acetate.
Bitartrate.
Chlorate.
Citrate.
Nitrate.

Hydragogue Diuretics.

Adonis Vernalis.
Broom.
Caffeine.
Colchicum.
Digitalis.
Erythrophlœum.
Nitrous ether.
Squill.
Strophanthus.

[1] Jendrássik, *Deutsch Archiv f. klin. Med.*, xxxviii. p. 499.
[2] Locke, *Practitioner*, xxxvii. p. 170.
[3] Riegel, *Verhandl. d. III. Congress f. inner. Med.*, 1884.
[4] Von Schroeder, *Central. f. d. med. Wiss.*, 1886, p. 465; Langgard, *ibid.* p. 513.

Stimulant Diuretics.

Alcohol.
- Gin.
- Hock.

Cantharides.
Blatta Orientalis.
Oleo-resins, resins and volatile oils—
- Turpentine.
- Juniper.
- Savin.
- Copaiba.
- Cubebs.
- Black pepper.
- Matico.
- Kawa.
- Guaiac.

Umbelliferous plants chiefly containing volatile oils—
- Parsley.
- Carrot.
- Dill.
- Fennel.

Cruciferous plants—
- Mustard.
- Horseradish.
- Asparagus.

Uva ursi.
Sarsaparilla.
Buchu.
Pareira.
Chimaphila.
Taraxacum.
Ononis spinosum.
Santonica.

The following tabular view of the probable mode of action of the various diuretics may help to show it more distinctly:—

DIURETICS.
- Raise arterial pressure....
  - Generally
    - Increased action of the heart — digitalis. alcohol.
    - Contraction of vessels in intestine and throughout the body. — Digitalis. Erythroph'œum. Strophanthus. Squill. Convallaria. Strychnine. Caffeine (p. 432). Cold to surface.
  - Locally in kidney.
    - Contract efferent vessels or arteriæ rectæ so as to raise pressure in glomerulus and lessen absorption in tubules, or both.
      - By action on vaso-motor centres. — ? The same as in preceding list.
      - By local action on vessels or nervous structures in the kidney itself. — ? Broom. ? Turpentine. ? Juniper. ? Copaiba. ? Cantharides.
    - Dilate afferent vessels.
      - Paralyse vaso-motor nerves or involuntary muscular fibre, or stimulate vaso-dilating nerves. — Nitrites. Alcohol. ? Urea.[1]
- Act on the secreting nerves, or secreting cells of the kidney itself.
  - Increase water excreted. — Urea. Caffeine. Calomel.
  - Increase solids excreted. — Liquor potassæ. Potassium acetate, &c., and other saline diuretics.

Uses.—Diuretics may be employed for the purpose of removing either **water** or **solids** from the body. They are used:—

1st, to remove the excess of fluid met with in the tissues and serous cavities in cases of dropsy.

2nd, to hasten the removal of injurious waste-products and poisonous substances from the blood.

3rd, to dilute the urine.

[1] When a current of blood is passed artificially through an excised kidney, the stream is much accelerated by the addition of urea. Abeles, *Sitz.-Ber. d. k. k. Wiener Akad.*, Bd. 87, Abt. 3, April 1883.

In cases where the accumulation of fluid depends on venous congestion, as for example in **cardiac** dropsy, those diuretics which act on the general vascular system, like digitalis, strophanthus, squill, or erythrophlœum, are most efficient because they tend to remove the cause of the dropsy (p. 333), as well as to assist the absorption and excretion of the fluid already effused.

When the dropsy depends on the disease of the **kidneys** or **liver**, other diuretics should either be given instead of, or along with, digitalis or squill. Even in cases of cardiac disease where digitalis or squill are not proving efficacious, the addition of a little blue pill greatly assists their action, though it would be hard to say in what way it does so.

In dropsy depending on kidney disease, decoction of broom, oil of juniper, and nitrous ether are amongst the most reliable diuretics, and in hepatic dropsy, copaiba.

Diuretics are used to increase the secretion of **solids** in febrile conditions, and in cases of kidney disease where the excretion of waste-products is deficient, and their retention threatens to prove injurious. In such cases nitrate and bitartrate of potassium, turpentine, juniper, and caffeine are useful.

Diuretics are also used to **increase** the proportion of **water** in the urine, and thus to prevent the solids being deposited from it and forming calculi in the kidney or bladder, or even to dissolve again such concretions as have been already formed.

Adjuvants to Diuretics.—As the amount of urine secreted depends upon the difference in pressure between the blood in the glomeruli and the urine in the tubules, it is evident that any pressure on the tubules, whether caused by obstruction of the ureter by a calculus, by the mechanical pressure of dropsical accumulations in the abdomen, or by distension of the venous plexus in the kidney itself, will tend to lessen the secretion of urine. Consequently we sometimes find that in such cases diuretics fail to act until the pressure has been relieved by **paracentesis** in cases of dropsy, or the venous congestion lessened by the use of a brisk **purgative**, or by **cupping** over the loins.

If the venous congestion is very great, as in cases of mitral disease or of chronic bronchitis with emphysema and dilated heart, bleeding from the arm may be advantageous or even imperatively necessary. In dilated heart and in mitral incompetence, the action of digitalis on the heart itself, strengthening its action and enabling it more effectually to pump the blood out of the venous into the arterial system and thus reduce venous congestion, will aid its action upon the kidneys.

Action of Drugs on Albuminuria.—In the normal kidney no albumen passes from the vessels or lymphatics into the urinary tubules, but under abnormal conditions it may do so and the urine become albuminous.

Albuminuria may be produced by ligature or compression of the renal artery; by ligature of the renal vein; and, though to a less extent, by ligature of the ureter. A similar effect to that of ligature of the renal artery may be produced by causing it to contract temporarily by means of drugs such as digitalis. In the experiments made by Mr. Power and myself we noticed that the urine which was secreted after the secretion had been completely stopped by digitalis was albuminous.

Albuminuria is also noticed after poisoning by strychnine, which, as Grützner has shown, has a similar action to digitalis, and in cases of suffocation or of epilepsy, where the vaso-motor centre is stimulated by venous blood.

Other drugs appear to cause albuminuria by a direct action on the kidney itself. A marked example of this is cantharides, which produces both albuminuria and hæmaturia. Shortly after its injection the kidney appears congested and swollen, and on microscopic examination it is found that the alterations begin first in the glomeruli and convoluted tubules, and gradually extend to the straight tubules. These changes consist in intense congestion, especially in the glomeruli, with increased tension of blood in the vessels. Then the liquid constituents of the blood pass through the vascular walls, carrying along with them granules, red corpuscles, and white corpuscles. This exudation then passes from the glomerulus along the whole length of the tubules, the epithelium of which next becomes changed, the cells which line them swelling up, multiplying, and becoming modified in form, migration of leucocytes also occurring. In short, we have the signs of inflammation beginning in the glomeruli and passing along the tubules.

Lead produces also disease of the kidney, but of a different kind. The kidney in animals poisoned by it is pale and granular with an adherent capsule and with atrophy of the cortical substance, in which crystals are often present. These appearances are due to chronic interstitial nephritis caused by calcareous deposits in Henle's loops. These block up the tubuli, produce subacute inflammation of the glomeruli and tubules, with atrophy and cirrhosis. A similar result is produced also by mercury. Chlorate of potassium has a very peculiar action on the kidney. In large doses it produces a peculiar kind of hæmaturia, the urine being dark brown and containing large quantities of broken-up blood-corpuscles. The drug arrests the secretion of the urine by blocking up the tubules with plugs of broken-up blood-corpuscles.

Tannin and tannate of sodium appear to have a certain power to lessen the exudation of albumen through the Malpighian tufts, as Ribbert found that when albuminuria was produced artificially in rabbits by temporary ligature of the renal artery, both tannin and tannate of sodium either lessened or

prevented the exudation of albumen. Arbutin, the active principle of uva ursi, appears to be still more efficacious, but requires to be given in somewhat large doses. Fuchsin has a similar action.

Lithontriptics.

These are remedies employed for the purpose of preventing the solids of the urine from being deposited, or of causing resolution.

One of the most important is the abundant use of water, and sometimes it is advisable to use distilled water in place of ordinary water, as distilled water is free from salts of any kind. Distilled water has a disagreeable, flat taste, but it may be made quite agreeable by charging it with carbonic acid in a gasogen.

The substances which most generally are deposited from the urine are uric acid, acid urates, oxalate of calcium, and phosphates; the two former are liable to be deposited when the urine is too acid, and the two latter when it is alkaline or neutral. Oxalate of lime also may be deposited from faintly acid urine. These substances may be deposited either in the kidney or bladder, and thus give rise to renal or vesical calculi.

The lithontriptics generally employed when uric acid, or acid urates are present, are salts of lithium and potassium, as the urate of potassium is more soluble than the urate of sodium, and the urate of lithium more soluble than even that of potassium. On account of the low atomic weight of lithium its salts have the further advantage of combining with a much larger relative proportion of uric acid than the salts of potassium or sodium. When phosphates are present, mineral acids, such as phosphoric, are sometimes employed, but it is difficult to render the urine acid by the internal administration of mineral acids, although it is easy to render it alkaline by the administration of alkalies. Benzoic and cinnamic acids, however, in passing through the body, are converted into hippuric acid, and they render the urine acid. They may either be given alone, or in combination with ammonia, as benzoate of ammonium, because, although ammonium is alkaline, yet it appears to undergo conversion into urea in the body, and does not render the urine alkaline.

The deposition of oxalate of calcium is usually connected with disturbances in the digestive system, and I have observed, in a hospital ward, that a deposit of it is very commonly found in the urine after the patients have had cabbage for dinner. The administration of nitro-hydrochloric acid frequently tends to prevent the deposition of oxalates, and this is, perhaps, on the whole, the best remedy for the form of dyspepsia to which the name of oxalic diathesis is sometimes given. Sometimes, however, carbonate of sodium, by aiding the digestion, seems to be more beneficial.

ACTION OF DRUGS ON THE SKIN.

Diaphoretics and Sudorifics.

The difference between these classes of remedies is simply one of degree. When a drug **increases** the secretion of **sweat** only slightly, so that it can still evaporate from the skin without running down in drops, it is called a **diaphoretic**; but when it increases it so greatly that it can no longer evaporate, and streams down the skin, it is called a **sudorific.**

The **secretion** of sweat, like that of saliva, consists in the formation of the secretion by the cells of the gland from the material which is yielded by the fluid in the lymph-spaces around the gland.

New material is constantly supplied to this fluid by the blood which circulates in the vessels. We therefore find that **increased circulation** of blood through the cutaneous vessels and increased secretion of sweat usually accompany one another, but this is not always the case. In the sweat-glands, as in the salivary glands, the **secreting nerves** which regulate the activity of the **cells** are independent of the vascular nerves which regulate the capacity of the vessels. In fever or in poisoning by atropine the vessels may be widely dilated and the current of blood through them **rapid,** while the **secretion** of sweat is arrested. On the other hand, in dying persons we see a copious secretion of sweat occur, while the circulation through the skin has become very feeble or almost stagnant. A certain amount of sweat, indeed, may even be secreted by amputated limbs, the material for it being afforded by the lymph around the glands. But profuse secretion of sweat cannot go on long unless the gland is freely supplied with blood, for otherwise the supply of new material would cease. Dilatation of the vessels therefore aids the secretion of sweat. Dilatation may be induced by section of vaso-motor nerves or stimulation of vaso-dilating nerves. Thus, when the sympathetic is cut in the neck of a horse, dilatation of the vessels is produced by the section, and sweating occurs on that side.

The vaso-dilating and secreting nerves of the sweat-glands usually run together, and by irritation of a nerve-trunk, such as that of the sciatic, the vessels of the foot may be dilated, and sweating excited.

Warmth usually increases both the circulation of blood in the skin and the secretion of sweat; while **cold** has the contrary effect.

The **nerve-centres** which excite the secretion of sweat appear to be situated in the **spinal cord**; the centre for the posterior

extremities being situated in the upper lumbar and lower thoracic part of the cord in the cat; while that for the upper extremities in the same animal is situated in the lower part of the cervical region of the cord.

The sweat-glands may be excited to secrete:

(1) By the action of drugs upon the terminations of nerves in the glands.
(2) By the action of drugs on the sweat-centres themselves.
(3) Reflexly by stimulation of sensory nerves.
(4) By mental stimuli.

An example of the stimulation of sweating by the action of drugs on the **nervous terminations** in the glands themselves is afforded by pilocarpine, which will cause secretion even when the nerves which connect the centres with the glands have been cut.

Secretion may be also arrested by the paralysing action of drugs upon the terminal fibres; thus, atropine, locally injected, prevents the secretion of sweat, however much the nerve going to the gland or the nerve-centres be stimulated; and atropine also antagonises the effect of pilocarpine on the nervous terminations, and arrests the secretion which the latter causes.

The **nerve-centres** may be stimulated directly by the condition of the blood which is passing through them, or reflexly by irritation of sensory nerves. Stimulants of these nerve-centres are: (1) a venous condition of the blood; (2) high temperature of the blood; and (3) poisons, especially nicotine.

A venous condition of the blood is one of the most powerful stimulants, and it is to this that the sweats which precede death are in all probability due; for while watching a patient dying, I have observed that drops of sweat appeared on the brow just at the time that the blood became venous, as was evidenced by the commencing lividity of the finger-nails and lobes of the ears. Under such conditions, while the secreting cells are strongly stimulated, the circulation is very feeble.

A high temperature is also a powerful stimulant. In considering its action we must take into account the effect of the warm blood upon the sweat-centres in the cord, as it circulates through them, and its local action also on the sweat-glands themselves. Up to a certain point it appears to have the effect of dilating vessels and of increasing the activity of the glands by acting both on the sweat-centres and on the periphery.

Local warmth to one foot increases the secretion of sweat, and local cold diminishes it in that foot, when the glands in all four feet of an animal are stimulated equally either by excitement of the sweat-centres or by the action of pilocarpine on the peripheral ends of the sweat-nerves.[1]

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[1] Luchsinger, *Pflüger's Archiv*, 1876, vol. xviii. p. 480.

The sweat-centres appear to be directly stimulated by nicotine, but the action of this drug may be partly due also to a reflex effect on those centres through the nerves of the stomach.

The sweat-centres appear to be **reflexly** excited by severe irritation of any sensory nerve passing from the surface of the body, and the point at which the irritation is applied does not seem to be of much importance. They are probably stimulated reflexly from the stomach, as in the sweating which accompanies nausea.

The power of the **brain** to stimulate the sweat-centres is shown in the effect of mental emotion, and direct irritation of the medulla oblongata will cause sweating in cats even some time after death.

Excretion by the Sweat-glands.—A number of substances taken into the body pass out in small quantities through the skin. Aromatic and volatile substances appear to pass readily, so also benzoic acid, hippuric and cinnamic acid, tartaric acid, succinic acid, iodide of potassium, quinine, corrosive sublimate, arseniates of sodium and potassium. When arseniate of iron has been taken, curiously enough, arsenious acid has been found in the sweat, and iron in the urine. Some **colouring matters** are excreted especially by the skin of the armpits, and the underclothing may sometimes be found stained of a brick-red colour at these parts. I have observed this in some cases after drinking claret or port, but it only occurs exceptionally after the employment of these wines, and it is possible that it is due to adulteration with foreign colouring matters, for I have also noticed it in cases where no wine has been drunk, but where pickled red cabbage or beetroot has been eaten.

Relations between Sweat-glands and Kidneys.—The sweat-glands and the kidneys both remove **water** and small quantities of salts from the blood, and thus tend to keep it at its normal concentration. Their functions are complementary, so that when much water is excreted by the skin, less is excreted by the kidneys, and *vice versâ*.

This complementary action is to a great extent due to the different distribution of blood under varying conditions, because when both organs are stimulated—as, for example, by salts of ammonium—diuresis will occur, if the blood be driven towards the kidneys by external cold; and diaphoresis if it be attracted to the skin by external warmth.

The quantity of solids contained in the sweat is very small—only a little over one per cent.—three-fourths of these being organic, and one-fourth inorganic. The organic solids are chiefly fats, fatty acids, and small quantities of urea—about one-tenth per cent. When the kidneys are insufficient, however, to excrete urea, the quantity in the sweat becomes greatly increased, and it has even been found crystallised upon the skin.

Action of the Skin in Regulating Temperature.—As I have already mentioned, the skin has an excreting function complementary to that of the kidneys, and it may to some extent relieve them when they are doing their work imperfectly. But its chief function is that of regulating the bodily temperature. The quantity of heat which is changed into potential energy, in converting liquid water into gaseous steam, is very great. Five and a half times as much heat is required to convert boiling water into steam as to raise the same amount of water from the freezing to the boiling point. The immense loss of heat thus occasioned converts the healthy skin under the influence of great heat into an actual cooling apparatus. In negroes on the West Coast of Africa it has been noticed that while the skin is perspiring profusely, it is as cold as marble, and Sir Charles Blagdon observed that in a room with a temperature of 198° Fahr. his side felt quite cold to the touch.

The chief **diaphoretics** are:—

Stimulating sweat-centres (?)	Ammonium acetate. ,, citrate. Dover's Powder. Ipecacuanha. Opium. Camphor.	
	Nicotine. Antimony.	Also reflexly through stomach (?) (p. 439).
Stimulating secreting nerves (?)	Pilocarpine. Warmth to surface, as in baths. Warm drinks. Alcohol.	
Doubtful action	Serpentaria. Sassafras. Guaiac. Mezereum. Senega.	

Uses.—Diaphoretics are used in cases of threatened catarrh or inflammation of mucous or serous surfaces, or internal organs after exposure to cold. Their beneficial action in such cases may be partly due to the withdrawal of blood from internal organs to the surface of the body, but it is not improbable that in addition to this the condition of the skin which they induce exercises a favourable action reflexly on internal parts. There seems to be a sort of complementary action between the skin and the internal mucous membranes, as well as between the skin and kidneys. This is sometimes well marked in gouty patients, where the disappearance of an eruption from the skin is followed by asthma, and *vice versâ*. It is also shown by the experiments of Rossbach (p. 252); and the effect of irritation of the stomach and nausea on the secretion of the skin has already been noticed (p. 439).

One of the best diaphoretics to cut short commencing catarrh is compound ipecacuanha powder. In fevers, with the exception of rheumatic fever, the skin is generally dry although the tem-

perature is high, and diaphoretics are employed to increase the cutaneous secretion, and thus to lower the temperature.

In exanthemata, after the eruption disappears from the skin, there is a tendency to inflammation of internal organs, and in order to prevent this, diaphoretics are used, those which act markedly on the vessels, or stimulating diaphoretics, being especially indicated.

The advantage of a free supply of blood in chronic morbid conditions, such as chronic ulcers, has already been mentioned when speaking of irritants (p. 343); and in chronic morbid conditions of the skin diaphoretics are sometimes employed to promote the cutaneous circulation. In diseases of the kidneys, when it is advantageous to lessen their functional activity, diaphoretics are employed in order to make the skin act vigorously; and they are used also to assist the kidneys in removing the fluid which has already accumulated in the body in cases of dropsy. When the kidneys, though not diseased, are called upon to do excessive work—as in diabetes mellitus, and polyuria—diaphoretics are employed to aid them. Where an unnatural secretion of fluid is taking place from the intestine, as in cases of chronic diarrhœa, diaphoretics are also employed to divert secretion from the intestine to the skin, and thus lessen the diarrhœa.

Antihidrotics or Anhidrotics.

These are substances which **lessen** the secretion of **sweat**:—

Acids.
Belladonna and Atropine.
Hyoscyamus.
Amanita muscaria and muscarine.
Agaricus albus.
Jaborandi and Pilocarpine.
Nux vomica and Strychnine.
Quinine.
Picrotoxine.
Ipecacuanha (compound powder).
Zinc salts.

These remedies may act (1) on the **sweat-glands** themselves by lessening the excitability either of the secreting **cells** or of the secreting **nerves**; (2) on the **sweat-centres**, by lessening their excitability or removing the excitant; and (3) on the **circulation**. Belladonna in large doses paralyses the ends of the secreting nerves, just as it does in the salivary glands, so that the sweat-glands will not secrete even when a strong stimulation is applied to their nerves. As belladonna acts thus when locally applied, it may be used for local sweating in the form of extract or of solution of atropine painted on, or rubbed over, the surface. It is thus useful in cases of local sweating of the palms of the hands and soles of the feet. It may also be given internally to paralyse the ends of the secreting nerves, and thus to arrest the night-sweats in phthisis. But in all probability its beneficial effect in

the night-sweats of phthisis is not dependent on its paralysing action on the secreting nerves, for it is useful in doses which appear too small to produce this effect, and which also do not act immediately, but rather after some time. Its utility in such cases, therefore, is probably due to an effect on the nerve-centres, and especially to a stimulating action on the respiratory centre.

The **night-sweats** of **phthisis** are usually followed by great weakness and prostration, which has sometimes been attributed to the loss of salts and organic matter contained in the sweat. But the quantity of these is very small, and the same depression is not noticed when there is an increase of two or three ounces

FIG. 153.—Diagram to illustrate the action of antihidrotics. The secretory nerves passing to the sweat-glands from the sweat-centres in the spinal cord have been represented as a single nerve for the sake of simplicity.

in the daily secretion of urine, although it will carry off quite as large a quantity of both salts and organic matter. Nor is the same depression produced by the profuse sweating due to active exertion, nor even by the sweating in ague. The depression is not the consequence of the profuse sweat; both are probably the consequence of one common cause. This cause I believe to be partial failure of the respiration and consequent accumulation of carbonic acid in the system, which leads at the same time to stimulation of the sweat-centres and impairment of tissue-change throughout the body generally.

In healthy persons the respiratory centre is more sensitive to the stimulus of carbonic acid than other parts of the nervous system. Thus any increase in the venosity of the blood at once stimulates this centre, and through it the diaphragm and respiratory muscles of the thoracic wall, rendering the respiration

more active, and increasing arterialisation. Consequently, the blood does not become venous enough to stimulate the sweat-centres. But when the respiratory centre is depressed by excessive reflex stimulation during the day in the process of coughing, and by the natural depression which occurs during sleep, it may respond less readily to the stimulus of venous blood. The amount of carbonic acid in the blood may thus accumulate to such an extent that the sweat-centres are stimulated before the respiratory centre responds, and thus the profuse sweats which are so depressing to the patient may occur.

It is probable that this is only part of the truth, and that there are other factors in the production of abnormally profuse sweats; for in children suffering from rickets, the head perspires profusely during sleep, yet the mucous membranes are of a bright rosy colour. Nevertheless, acting on this idea, I have given at night such substances as are powerful stimulants to the respiratory centre, like nux vomica and strychnine, and I have found that the sweating is usually arrested by them. A small dose is sometimes sufficient, but occasionally it must be steadily increased until as much as half a drachm of the tincture of nux vomica is given at once. The only disadvantage that I have noticed from this treatment is that the excitability of the respiratory centre sometimes persists during the day, and renders the cough more troublesome. I have tried to remedy this by combining strychnine with opium, and partially succeeded. If we now review the **remedies** used in the **night-sweating** of phthisis, we shall see that almost every one of them has a **stimulant** action on the **respiratory centre.** This is possessed in a marked degree by atropine and hyoscyamus. Ipecacuanha has this action also, and its combination with opium, in the form of Dover's powder, although it causes sweating in healthy persons, tends to restrain it in phthisical patients. Picrotoxine, salts of zinc, and pilocarpine, all stimulate the respiratory centre also, and we find that the last is useful in the night-sweats of phthisis, although we should expect from its physiological action that it would be injurious, stimulating, as it does, the terminations of the secreting nerves in the sweat-glands themselves. It is possible, however, that in addition to the stimulation of the sweat-centres by venous blood, the night-sweats of phthisis may be sometimes increased by the **high temperature** of the patient, and in such cases quinine, as Murrell has pointed out, is likely to be most serviceable.

ACTION OF DRUGS ON THE BLADDER

The walls of the bladder consist of involuntary muscular fibre which expels the urine by its contraction. Around the neck of the bladder is a band of involuntary muscular fibre, the

sphincter vesicæ, which by its contraction closes the orifice and prevents the escape of urine. The sphincter vesicæ receives its motor supply through the third, fourth, and fifth sacral nerves.

The **nerve-centre** for the movements of the bladder is situated in the **spinal** cord opposite the fifth lumbar vertebra in dogs, and the seventh in rabbits. This centre is able to regulate the retention and discharge of the urine by the bladder even when the spinal cord is divided between it and the brain, but the activity of the centre under normal conditions is modified by the brain, so that we may consider that there is a cerebral as well as a spinal centre for the bladder. The spinal centre may be set in action either reflexly, or by stimuli passing down from it to the brain. The cerebral centre may be set in action either reflexly or voluntarily.

Usually when the pressure of the urine within the bladder is increased beyond a certain limit depending not only on the quantity of the water, but on the state of the contraction of the bladder itself, the neck of the bladder becomes slightly dilated, and a drop of urine exuding acts as a stimulus to the sensory nerves of the urethra, and thus calls reflexly into action the centre in the spinal cord by which at the same time the sphincter vesicæ is inhibited, and the detrusor urinæ stimulated. Reflex action may also be induced by stimulation of other nerves, as for example by the application of a wet sponge to the anus or perinæum. The **cerebral centre** is usually called into action by the sensation of the bladder being full. It may be called into action voluntarily, although there is little urine in the bladder; and also may be excited by emotion, such as fear.

It may be also excited reflexly through the sense of hearing. Boerhaave was accustomed, when patients found difficulty in passing water, to make an attendant pour water from a height into a basin in the patient's hearing. The splashing thus occasioned induced the patient to pass water, and a similar effect, as is well known, is produced on horses by whistling. Nervous agitation has often the contrary effect of producing retention of water. When it is desirable for a person to pass water—e.g. when a specimen of urine is wanted for examination—it is advisable to put him in a room by himself and turn on a tap within his hearing. The removal of the restraint exercised by the presence of another person, along with the stimulant action of the sound of falling water, rarely fails to produce the desired effect. Even the recollection of the sound of falling water will tend to cause evacuation of the bladder, and when there is difficulty in passing water the patient may sometimes obtain relief by thinking of a waterfall. Washing the hands in cold water also tends reflexly to cause evacuation of urine, and the effect of a wet sponge to the perinæum has already been mentioned.

Vesical sedatives are substances which lessen the irritability

of the bladder, and thus remove pain, and lessen the desire to urinate. This desire may be excited not only by the presence of urine in the bladder, but by the irritation of calculi, or inflammation of the mucous membrane of the bladder itself. When calculi are a source of irritation, carbonate of calcium taken internally seems to lessen the irritability. In cystitis the irritation is diminished by the use of very hot water externally, in a bidet or hip-bath. The irritability of the nerves may be diminished by opium, belladonna, and hyoscyamus, and by drinking freely of warm water, either alone or in the form of an infusion or decoction of some mucilaginous substance, e.g. linseed-tea or barley-water.

In chronic inflammation the irritation may be diminished by astringents such as buchu, uva ursi, pareira brava, and alchemilla. **Vesical tonics** are substances which increase the contractile power of the muscular fibres in the bladder. They are therefore useful in two different conditions, for by strengthening the detrusor urinæ they prevent retention, and by strengthening the sphincter vesicæ they prevent incontinence.

Some of these remedies appear to act by increasing the stimulating power of the urine, so that the sphincter vesicæ is consequently more firmly contracted; of this class is cantharides. Others appear to alter the direction of reflex action; such are the passing of a bougie through the urethra once or twice a day, or the application of an injection of nitrate of silver, ten to thirty grains to the ounce, to the neck of the bladder. Others act on the nerve-centres and apparently are useful sometimes by lessening the reflex susceptibility from the bladder, so that the detrusor urinæ is less called into action; at other times by increasing the susceptibility of the nerve-centre, so that the sphincter vesicæ is more firmly contracted—of the latter class is strychnine; to the former belongs bromide of potassium, which must be given at night. Belladonna, which is one of the most useful remedies in incontinence of urine, acts upon the nerve-centres, but whether it acts in the same way as strychnine or as bromide of potassium, it is difficult to say. It is quite possible that it lessens the sensibility of the bladder to changes of pressure within it in somewhat the same way as it lessens the sensibility of the heart to changes in blood-pressure (p. 298).

Urinary Sedatives and Astringents.

When the urinary passages are healthy, the secretion of mucus from them is very slight, and the presence of urine in the bladder or its passage along the urethra usually gives rise to no pain. Pain and scalding are sometimes caused by an abnormally acid urine, or by the presence of crystals of uric acid

in it, even though the mucous membrane itself be healthy. In such cases the use of potash or lithia is indicated to restore the healthy character of the urine.

When the bladder itself is irritable or inflamed, the secretion of mucus is increased and there is constant desire to micturate. There are here two indications to be fulfilled: one is to lessen the irritability, and the other is to remove the inflammation. In lessening the irritability, belladonna seems to be especially useful, and to diminish the inflammation, astringents are employed.

In inflammation of the urethra the same indications exist, and here also cubebs, copaiba, and sandal-wood oil are employed. It is, however, easier to apply astringents locally to the urethra than to the bladder, and consequently astringent injections are more frequently used: these are usually solutions of alum, sulphate or acetate of zinc, and acetate of lead.

Finely-divided powders act also beneficially by keeping the inflamed walls of the urethra apart, and on this account a mixture of sulphate of zinc and acetate of lead, which gives a fine, white, insoluble precipitate of sulphate of lead, is more efficacious than either of the solutions employed alone. Kaolin or china clay, which is a completely inert powder, as well as bismuth and calomel, have also been used for a similar purpose. As it is found that the secretion in gonorrhœa frequently, if not always, contains microscopic organisms, the injection of antiseptics has been used: among these may be mentioned permanganate of potassium and zinc, boric acid, carbolic acid, sulpho-carbolates, sulphurous acid, as well as drugs having both an astringent and antiseptic action, like chloralum, perchloride and pernitrate of mercury, and chloride of zinc.

The beneficial effects of copaiba in inflammation of the bladder and urethra are probably due to its antiseptic action. It is excreted in considerable quantities by the kidneys and renders the urine antiseptic, so that its decomposition and the appearance of bacteria in it are greatly retarded or completely prevented. The whole urinary passages from the glomeruli of the kidney to the orifice of the urethra are thus washed out by antiseptic urine, which does not decompose, and which tends to destroy or remove any germs that may be present. Cubebs, terpenes,[1] and naphthalin[2] have probably a similar action.

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[1] Schmiedeberg, *Arzneimittellehre*, p. 121.
[2] Rossbach, *Berlin. klin. Wochenschr.*, 1884, No. 46, p. 279.

CHAPTER XVI.

ACTION OF DRUGS ON THE GENERATIVE SYSTEM.

Aphrodisiacs and Anaphrodisiacs.

THE sexual function is regulated by two nerve-centres, one of which is cerebral and the other spinal. The **cerebral centre** is the seat of the feelings and appetite which prompt the individual to seek sexual congress.

The **spinal centre** regulates the condition of erection in the sexual organs which is necessary for coitus. These two centres may act independently of each other, e.g. when the spinal cord is cut, but in the normal condition they naturally influence each other, excitement of the spinal centre re-acting on the cerebral centre so as to awaken sexual feelings, and excitement of the cerebral centre re-acting on the spinal so as to produce erection of the genital organs.

Erection is due partly to dilatation of the arteries in the erectile tissues of the genital organs, and partly to compression of the efferent veins. The blood being thus allowed to flow freely into the organs, and prevented from flowing out, distends them so as to render them turgid and more or less rigid. During the orgasm the turgidity is increased by partial stoppage of respiration, which, by rendering the blood venous and thus stimulating the vaso-motor centre, tends to raise the blood-pressure in the body generally, and in the erectile tissues particularly.

Dilatation of the arteries in the genital organs and consequent erection occurs on stimulation, either of the genital centre in the lumbar spinal cord or of the vaso-dilating nerves (nervi erigentes) which pass from it to the genital organs and end in a ganglionic plexus surrounding the arteries.

The **lumbar** genital centre may be excited either reflexly by stimulation of the sensory nerves of the genital organs and adjoining parts, or by psychical stimuli transmitted to it from the brain.

The exact seat of the cerebral genital centre has not been determined, but Eckhard has found that irritation of the crura

cerebri can produce similar effects to stimulation of the nervi erigentes.

The **cerebral** genital centre may be stimulated and sexual feelings aroused by impressions made on the nerves of special

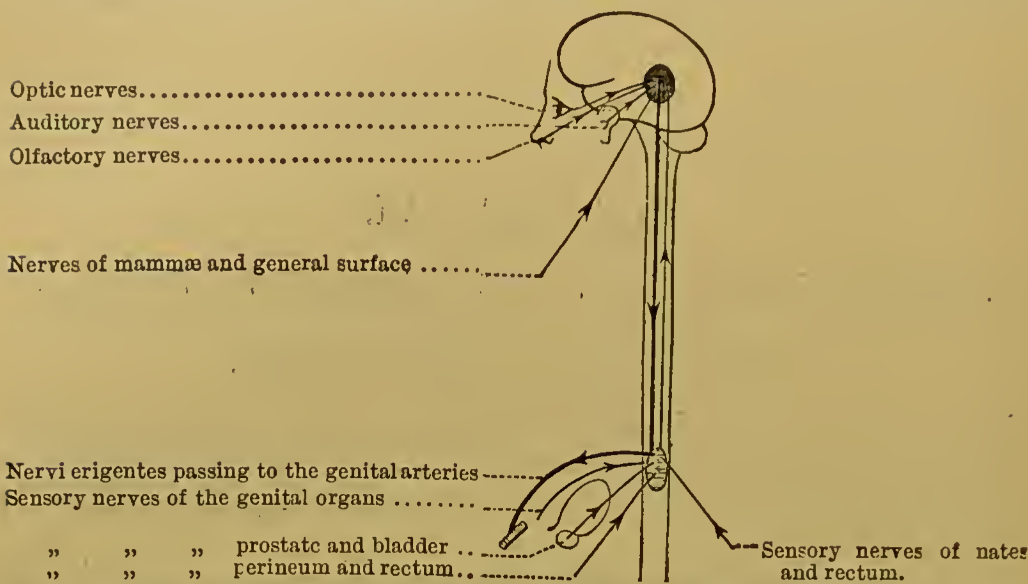

FIG. 154.—Diagram to illustrate the action of aphrodisiacs and anaphrodisiacs. The darkly-shaded spot indicates the genital centre in the brain, and the lighter spot the spinal centre in the lumbar portion of the cord. The direction in which impulses are conveyed along the nerves are indicated by the arrows. The nerves from the general surface have been represented as going to the cerebral centre, and acting through it on the spinal centre. It is probable, however, that several of them pass directly to the spinal centre, as represented in the case of the nerves of the nates.

or general sense, e.g. on the eye, ear, nose, on the mammæ, and general surface of the body, the genital organs and parts adjoining, as the bladder, prostate, and nates. Thus, sexual excitement may occur in consequence of the sight of persons or pictures, the reading or hearing of licentious stories, or of irritation of the surface of the body either by gentle friction or by pruriginous irritation due to irritating articles of clothing, parasites, or skin diseases. Distension of the bladder has a somewhat similar effect, and the irritation consequent on an enlarged prostate is probably, in part at least, the cause of the great sexual excitement which sometimes occurs in elderly men. A very acid condition of the urine, such as is found in some gouty patients, may possibly have a similar action. Chlorate and nitrate of potassium administered internally are said by Jacobi[1] to render the urine so irritating and to produce such sexual excitement as to lead to onanism. Ascarides in the rectum may cause excitement of the cerebral genital centre and give rise to nocturnal emissions as well as possibly to diurnal excitement, and in females they may cause even greater irritation by passing into the vagina. Irritation of the rectum from the presence of piles or fissure may also give rise to such great sexual excitement as to induce onanism or nymphomania. Fæces in the rectum, and perhaps in the

[1] *Medical Times and Gazette*, 1876, vol. i. p. 177.

colon, may also cause sexual excitement in some persons or increase it when present.

Such sources of local irritation may sometimes be insufficient to affect the cerebral centre during waking hours, when the attention is otherwise engaged, but may do so powerfully during sleep, or when the cerebral functions are disturbed by cannabis indica, and they may then produce erotic dreams or seminal emissions.

The lumbar centre is most readily excited by mechanical stimulation of the genital organs, but it may be also powerfully stimulated from the mucous membranes of the urinary passages, as is seen in the painful priapism which occurs in poisoning by cantharides.

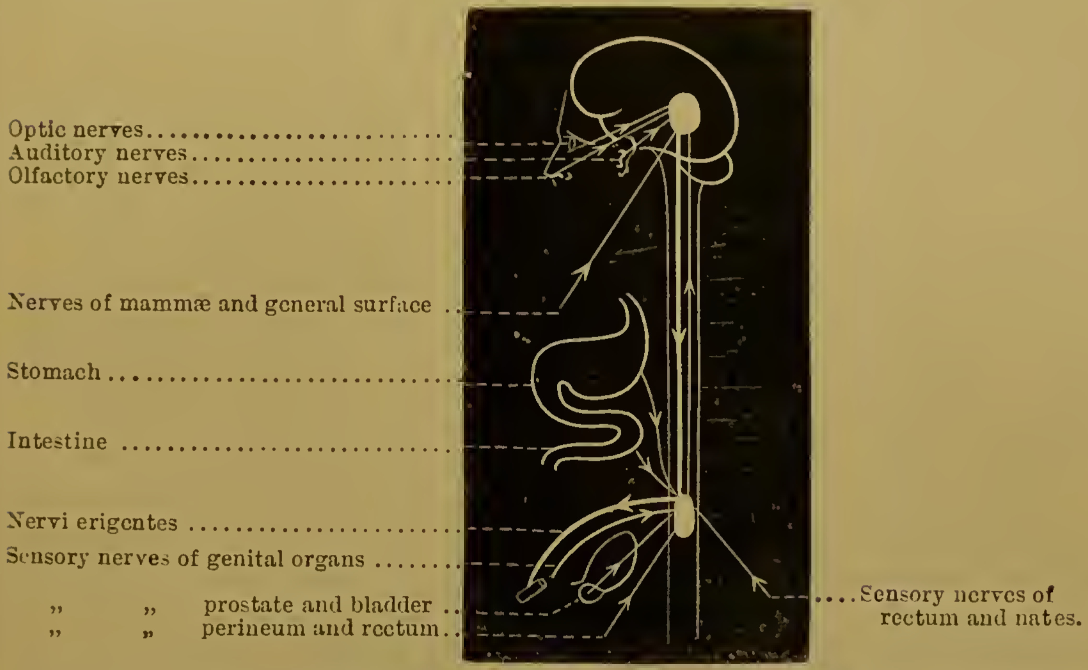

FIG. 155.—Diagram to illustrate the effects on the genital centres of irritation of the stomach or intestine by flatulence, acrid matters, or fæcal accumulations.

Stimulation of the lumbar centre without stimulation of the cerebral centre may occur from the presence of fæces in the rectum and perhaps in the colon, so as to give rise to seminal emissions during sleep unaccompanied by any dreams of a sexual character. Distension of the stomach or intestines by flatus may have a similar effect (Fig. 155).

Aphrodisiacs.

These are medicines which increase the sexual appetite.

Irritation of the nates, either mechanically alone, by flogging, or mechanically and chemically combined, by urtication or flogging with nettles, has been used as an aphrodisiac.[1]

[1] Trousseau et Pidoux, *Traité de Thérapeutique.*

The sexual function requires, however, for its proper performance a healthy state of the body, and good, or at least fair, nutrition; without these mere reflex excitement of the genital centres is likely to prove inefficient for the propagation of the race. Tonics generally, such as iron, are therefore to be regarded as indirect aphrodisiacs.

Strychnine has probably a double action, both increasing the general nutrition and rendering the genital nervous centres, both lumbar and cerebral, more susceptible to the action of stimuli. Its aphrodisiac action is sometimes an objection to its use as a tonic, for both it and nux vomica may cause seminal emissions which more than counterbalance its tonic action and weaken the patient.

Cannabis indica has been regarded as an aphrodisiac, but the trials of it made in this country seem to show that it does not itself at least have any such action, and merely induces a condition of partial delirium in which Easterns may possibly have visions of a sexual nature, and indeed, they try to give a sexual direction to the mental disturbance which the cannabis produces, by mixing with it musk, ambergris, or cantharides.

Catharides act as an aphrodisiac, but their action is probably due to an irritating effect on the mucous membrane of the urethra, and their use in such doses as to have any aphrodisiac action is attended with danger. Blatta orientalis when used as a diuretic may have an aphrodisiac action like cantharides.[1]

Alcohol appears to excite the cerebral centre and increase the sexual appetite, while it interferes with the proper performance of the generative act.[2] This interference may be due to partial paralysis of the lumbar centre or the nervi erigentes; but paralysis of the vaso-motor centre is probably a potent factor, or may indeed be the only cause of the impotency produced by alcohol; for alcohol paralyses the vaso-motor centre to such an extent that it will not react to the stimulus of venous blood, and even suffocation will not raise the blood-pressure.[3] Consequently, the rise in blood-pressure which holding the breath will normally produce during coition (p. 447) will not occur when much alcohol has been taken, and the penis, although it may be turgid from dilatation of the vessels, will not acquire the rigidity necessary for the generative act.

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[1] Buttenwieser, *Der practische Arzt*, Feb. 1882.
[2] Shakespeare, *Macbeth*, act ii. scene 3.
[3] Dogiel, *Pflüger's Archiv.* vol. viii.

Anaphrodisiacs.

These are medicines which diminish the sexual passion.

The agents employed as anaphrodisiacs are :—

Ice.	Conium.
Cold baths, local and general.	Camphor.
	Digitalis.
Bromides of potassium and ammonium.	Purgatives.
	Nauseants.
Iodide of potassium.	Bleeding.

Anaphrodisiacs may act locally on the genital organs, or may act upon the genital nerve-centres.

The effect on the nervous system may be directly exerted on the nervous structures themselves, on the circulation, nutrition, and general surroundings. Amongst the most powerful local anaphrodisiacs is the continuous application of cold by means of ice. Bromide of potassium possibly has also a local as well as a general action.

When the lumbar portion of the cord is abnormally stimulated reflexly, the stimulus ought to be removed : thus, in warm countries, where smegma may accumulate around and irritate the glans penis, very careful washing is requisite and circumcision is an advantage. Both in warm and cold countries circumcision, either general or partial, is useful if the prepuce be very long and its orifice much contracted.

When the irritation appears to arise from the presence of very acid urine, or of crystals of uric acid, irritating the bladder or urethra, as in gouty persons, potash or lithia should be employed to lessen the acidity of the urine, or to render it neutral. Where abnormal irritation of the genitals is present the urine should be examined for sugar as well as for uric acid, as the sugar may cause local irritation of the prepuce or vulva.

Distension of the bladder ought also to be avoided, and in persons who suffer from seminal emissions, occurring in the morning, it is occasionally advisable that they should be awakened and empty the bladder an hour or more before their usual time of rising.

If stone in the bladder is acting as an irritant, surgical treatment should be employed, but in cases where this is inadvisable, or where the irritation is dependent on enlarged prostate, general anaphrodisiacs must be used, such as bromide of potassium in large doses, care also being taken that the condition of the urine is not abnormally acid or alkaline. Ascarides in the rectum must be treated with anthelmintics. When irritation arises from piles the use of sulphur internally is often beneficial, though surgical interference may be necessary both for them and for fissure.

When irritation arises from fæcal accumulations in the rectum or colon, they should be removed and their return prevented by the careful use of aperients.

Flatulent distension of the stomach or intestines may be removed by alkalis and cholagogues, bitters (p. 378), and especially by strychnine, which gives tone to the intestine. It thus happens that, notwithstanding the tendency of strychnine to cause sexual excitement and produce emissions by its action on the nerve-centres, it may sometimes effectually relieve these conditions by its action on the intestine.

As anything which tends to increase the flow of blood to the genital organs or the lumbar portion of the spinal cord heightens their excitability, care should be taken not only to avoid this, but also to direct as much as possible the current of blood to other parts of the body. Thus, warm and heavy clothing or pads about the hips or loins should be avoided, and a hard mattress should be used in the place of a feather bed. Sometimes patients suffer from emissions in consequence of lying on their back. This is probably due to the effect of warmth on the spinal cord, and in order to avoid it, a towel or girdle should be put around the loins with a knot tied in it, or some hard substance fastened on it opposite the spine, so that the person would, even during sleep, be prevented from lying on his back. Walking exercise is not so useful as exercise of the arms, as in rowing, gymnastics, or mechanical occupations, such as those of a carpenter or blacksmith, because, in walking, the current of blood passes towards the lower extremities and part of it may become directed to the pelvis. In the other occupations just mentioned, the current of blood is, on the contrary, directed to the upper extremities. Working a treadle, as in turning a lathe or sewing-machine, is objectionable, both because the blood is directed towards the lower extremities generally and because it may become specially directed to the genitals by occasional friction of the clothes.

Hard mental work has also a similar effect to that of bodily exercise. In addition to these measures, a meagre diet, and especially a vegetable diet, with the avoidance of stimulants, is of considerable service.

Emmenagogues and Ecbolics.

Emmenagogues are remedies which **restore** and regulate the normal **menstrual flow** when it is absent or deficient or irregular.

Ecbolics are remedies which cause the **expulsion** of the **contents** of the **uterus.**

In menstruation both ovaries and uterus become congested. An ovum is discharged, and a flow of blood occurs from the

uterus. Diminution or absence of the menstrual flow may be occasioned either by general or local conditions: thus great debility or anæmia may cause it, and it is very frequent indeed in the anæmia and debility which are consequent on the occurrence of slight consolidation in the lungs.

A local cause may be deficient determination of blood to the ovaries and uterus, although no general anæmia exists.

The remedies employed for these two conditions are termed **indirect emmenagogues.** To correct anæmia, iron, manganese, and cod-liver oil may be employed.

In order to determine more blood to the uterus, warm foot-baths, warm hip-baths, mustard hip-baths, mustard stupes or poultices to the thighs and lower part of the abdomen, and leeches to the inside of the thighs or to the genitals, and aloetic purgatives, may be employed.

It might at first seem from theoretical considerations that foot-baths could hardly have any action on the uterus, but warm foot-baths cause great dilatation of the arteries in the legs, and it is probable that this dilatation extends up the iliacs, so that more blood may be sent to the genitals as well. But in addition to this, it is not at all improbable that a close nervous connection exists between the vascular supply of the uterus and of the feet, for not only does the warm foot-bath tend greatly to restore, but cold and wet feet are amongst the most powerful agents in checking, menstruation.

Other substances, which seem to have a direct stimulating action upon the womb itself, are called **direct emmenagogues.** It is not easy to see at present how they act; we know, however, that when given in large doses they cause contraction of the womb, and thus act as ecbolics. The chief emmenagogues are:—

Indirect Emmenagogues.

- Baths — Hot foot. / Hot hip. / Mustard.
- Leeches — To genitals. / To thighs.
- Mustard — Baths. / Poultices. / Stupes.
- Purgatives, as aloes.
- Iron.
- Manganese.
- Cod-liver oil.
- Strychnine.

Direct Emmenagogues.

- Ergot.
- Digitalis.
- Savin.
- Quinine.
- Asafœtida.
- Myrrh.
- Guaiacum.
- Cantharides.
- Borax.
- Rue.
- Hydrastis.[1]

[1] Fellner, 'Die physiolog. Wirkung einiger Präparate des Hydrastis Canadensis.' *Wien. med. Jahrbücher*, 1885.

Ecbolics.

The involuntary muscular fibres of the uterus appear, like those of the ureter or of the frog's heart, to possess the power of rhythmical contraction, and may contract when entirely separated from the general nervous system. They are, however, controlled by the higher **nerve-centres**. There appears to be one centre, situated in the **lumbar** portion of the spinal cord, which is of itself sufficient to regulate all the movements, for they go on normally, even when the spinal cord has been completely divided above it. This **centre** may be reflexly stimulated and contractions of the uterus induced by irritation of the ovarian, crural, or sciatic nerves. It may be also stimulated by the action upon it of drugs circulating in the blood, as ergotin, picrotoxine, or strychnine, or by great venosity of the blood, due to asphyxia.

There appears, however, also to be a second centre for the uterus, as for the male genital organs, in the **brain** (*vide* p. 448), by which the lumbar centre may be excited, and in consequence of this, stimulation of the cerebellum, crura cerebri, corpora striata, and optic thalami, also gives rise to uterine contractions.

Von Basch and Hofmann consider that the impulses pass to the uterus from the central nervous system, along two sets of nerves. One is composed of nerves passing from the inferior mesenteric ganglion to the hypogastric plexus. Stimulation of these causes circular contraction of the uterus, descent of the cervix and dilatation of the os. The other consists of branches passing from the sacral nerves across the pelvis to the hypogastric plexus, and representing the nervi erigentes. On stimulation of these the uterus contracts longitudinally; the cervix ascends and the os closes.

The mode of action of ecbolics has not been satisfactorily ascertained. Ammonia injected into the circulation appears to cause contraction of the muscular fibres, for it causes contraction of the uterus even when all nervous connections have been divided. Ergot possibly acts in the same way, but it is possible also that it acts on the spinal centre.

The chief ecbolics are:—

Ergot.
Hydrastis.
Quinine.
Savin.
Thuja.

Uses.—Ecbolics are used to **accelerate** the **expulsion** of the child when the passages are free but expulsive power is deficient, and to cause firm contraction of the uterus and so **prevent hæmorrhage** after delivery.

Adjuncts.—Compression of the uterus by kneading, pressure over it by a pad, the hand dipped in cold water laid over the uterus, or a cold pad. Sternutatories have been used to supplement the expulsive power of the uterus, and when necessary, operative interference must be had recourse to.

The injection of hot water into the vagina, as hot as can be borne, is a great aid in causing firm contraction of the uterus, and thus stopping *post partem* hæmorrhage. Some of the liquid probably enters the cervix through the flaccid os (*vide* p. 351).

Action of Drugs upon the Mammary Glands.

The milk-glands somewhat resemble the salivary glands in the way in which they are affected by the central nervous system, and by the action of drugs upon them. The action of the central nervous system on the milk-glands, however, has not been made out with anything like the same clearness as in the case of the salivary glands, experiments on animals not having given very definite results. It is chiefly inferred from the effect of mental emotions in checking or altering the secretion of the milk; and from the effect of belladonna locally applied in checking the secretion. The amount of secretion appears to depend on the amount of blood-pressure in the gland, and gentle stimulation of the nipple increases both the flow of blood to the gland and the secretion of milk. It is uncertain whether there are definite secreting nerves affecting the gland-cells apart from the vaso-motor nerves.

The character of the milk depends to a great extent upon the feeding and exercise of the mother, and diet is the most important agent in regulating both the quality and the quantity of the milk. As Dolan points out, it not unfrequently happens that a wet nurse, when first she arrives, yields such milk that the child she is nursing thrives well, but the quality soon falls off. In place of much outdoor exercise and plain, nutritious diet, she is fed luxuriously and gets little exercise. In order to restore the quality of the milk in such a case, the woman must be restored as far as possible to her previous conditions of diet and exercise.

Many substances are excreted in the milk, such as ammonia and the aromatic oils to which vegetable substances belonging to Umbelliferæ and Cruciferæ owe their flavour, probably also all volatile oils are thus excreted. Amongst those which have actually been found to pass into the milk are the oils of anise, cumin, dill, wormwood, and garlic, as well as turpentine and copaiba. The purgative principles of rhubarb, senna, scammony, and castor-oil, pass into the milk. Opium, iodine, and indigo do so also, and metals, such as antimony, arsenic, bismuth, iron, lead, mercury, and zinc. Volatile oils, having an agreeable taste,

do not appear to affect the secretion of milk directly, but appear to render it pleasant to children, so that they take the breast eagerly. When lactation is defective they may increase the reflex stimulus to the nipple by making the child suck more vigorously and thus increase the quantity of milk. For this reason such volatile oils as anise and dill may be useful as galactagogues. Garlic, on the contrary, renders the milk disagreeable to children, so that they will not take it. Copaiba also renders the milk disagreeable. The nearest approach to a true galactagogue is jaborandi, but it affects the gland only temporarily. Beer and porter stimulate the secretion for a short time, but they produce no proportionate benefit in the child, and nursing mothers are, as a rule, much better without alcohol, and should rather take milk instead. When the milk of the mother is deficient in saline constituents they may be supplied by giving the appropriate salts to the mother.

Various physiological actions may be produced in the child by administering drugs to the mother. The administration of acids to nursing mothers is generally to be avoided, as they are apt to cause griping in the child. Neutral salts as a rule pass into the milk and cause looseness of the bowels in the child. Senna, castor-oil, rhubarb, scammony, sulphur, and probably jalap, act as purgatives to the child. Salts of potassium administered to the mother will act as diuretics to the child. Turpentine administered to the mother also can be detected in the urine of the child; and this is also the case with copaiba and iodide of potassium. Opium administered to the mother may act as a narcotic to the child, and mercury, arsenic, and iodide of potassium may all be given to nursing children by administration to the mother.

CHAPTER XVII.

METHODS OF ADMINISTERING DRUGS.

Drugs may be used either for their local or general action, and sometimes for a combination of the two. Thus a solution of opium may be applied to the eye for its local effect in relieving irritation of the conjunctiva. It may be given by the mouth or injected under the skin to relieve pain and induce sleep, though the seat of the pain may be far removed, both from the point of injection and from the alimentary canal; or the opium may be applied in the form of a pessary in uterine disease to relieve pain, both by its local action on the part, and its general action on the system after absorption.

In order to produce their general action drugs may be introduced into the system through the skin, subcutaneous cellular tissue, lungs, mucous membranes, especially that of the alimentary canal, serous membranes and veins. The same drug applied in the same quantity through different channels may have different effects; for not only may slower absorption give rise to difference in the amount present at any time in the blood, as already explained (p. 38), but a reflex effect upon the organism may be produced by the local action of the drug at the place of introduction.

Application of Drugs by the Skin.

There are three different methods of applying drugs by the skin which are well recognised, these are :—

1. Epidermic, to the skin covered by epidermis.
2. Endermic, to the skin denuded of epidermis.
3. Hypodermic, to the subcutaneous cellular tissue.

Epidermic Application.—Remedies are applied to the unbroken skin chiefly for their local action on the part to which they are applied, or their reflex action through the nervous system on more distant parts. The epidermic applications are comparatively rarely used as a means of introducing drugs into the system, for the epidermis opposes such an obstacle to absorption, that it takes place slowly and with great difficulty.

In some of the lower animals, such as frogs, respiration takes place to such an extent through the skin, that the animal will live for a long time after respiratory movements have ceased. Respiration also takes place through the skin in man, but to a

very slight extent, the absorption of oxygen and the excretion of carbonic acid being only about $\frac{1}{200}$th part of that in the lungs.

The skin is able to absorb other gases as well as oxygen, such as sulphuretted hydrogen, carbonic acid, carbonic oxide, and the vapours of hydrocyanic acid, ether, and chloroform.

From the relief which persons who have been shipwrecked and have suffered from extreme thirst have received by bathing in sea-water, or putting on shirts wet with sea-water, it seems probable that the skin is able to absorb water, but this fact also shows that solids dissolved in the water are not absorbed by the skin. A good deal of discussion has taken place regarding the absorption by the skin of substances applied to it in a state of solution. Experiments on this point have usually been made with iodide of potassium, on account of the ease with which this salt can be detected in the urine. The results have generally been negative, but sometimes they have been positive. The general result is that the salt is never absorbed by the skin from the solution, and that in the cases where absorption has taken place, it has been due to the skin not having been washed after the bath, so that the iodide has crystallised on the surface, and has afterwards by friction of the clothes been rubbed into the sebaceous glands. It would appear that the fat in the skin as well as the epidermis presents an obstacle to the absorption of substances in solution, but when they are applied in such a form that they can readily mix with the sebaceous matter of the skin, they are tolerably readily absorbed, as for example when they are used in the form of ointment and well rubbed into the skin, so as to penetrate into the sebaceous follicles and also the sweat-glands. They are also absorbed when dissolved in ether, and especially in chloroform, even when simply painted over the surface. Alcoholic solutions are not absorbed when painted on in this way, although they may be absorbed if rubbed well in. It has been supposed that the absorption of chloroform solution is due to the chloroform mixing with the sebaceous matter. But, if true at all, this is certainly not the complete explanation of the fact, for as has just been mentioned, alcoholic solutions are not absorbed, although alcohol as well as chloroform will dissolve sebaceous matter. Waller has also shown that chloroform passes rapidly through the dead skin, carrying with it alkaloids dissolved in it. Its action is therefore to a great extent due to its peculiar endosmotic power.

The vascularity of the skin greatly alters its absorptive power. In the frog, absorption usually occurs rapidly through the skin, so that if the hind legs be immersed for a few minutes in a solution of cyanide of potassium, the salt is rapidly absorbed and can be detected in the mouth of the animal in a few minutes. But if the circulation be depressed by the previous administration of ether, curare, or any cardiac depressant, this absorption into

the system does not take place; for although the cyanide of potassium passes through the skin, yet, the subcutaneous circulation being feeble, it is not conveyed away from the point of local application into the system generally.

The absorption of drugs may therefore be diminished by depression of the circulation either locally at the point of application or in the system generally. It may be rendered more rapid by increased circulation at the point of application. A general increase in the circulation usually accelerates the circulation in the different parts of the body, but does not necessarily do so, for the vessels of a part may remain contracted while the general circulation is more rapid than usual.

A local increase in the circulation occurs from inflammation of a part, or from temporary irritation such as that produced by rubbing, or by the application of irritant substances. The use of friction, therefore, increases absorption not only by pressing the substances employed into the sweat-glands and hair-follicles but also by increasing the circulation, and this effect will take place to a still greater extent if the substances used have a tendency to cause dilatation of the vessels.

The most common methods of applying drugs epidermically are baths, poultices, inunction, and friction.

Baths.

These may be either **local** or **general**. In **general** baths, the whole of the body excepting the head is exposed to the action of various agents. According to the nature of the agent, baths may be divided as follows:—

I. WATER.
- A. Simple.
  - Cold.
    - (1) Ordinary full bath.
    - (2) Affusions.
    - (3) Spray.
    - (4) Sitz-bath.
    - (5) Foot-bath.
    - (6) Cold pack.
    - (7) Compresses.
    - (8) Douches.
  - Hot.
    - (1) Tepid bath.
    - (2) Warm bath.
    - (3) Hot bath.
    - (4) Hot foot-bath.
    - (5) Hot sitz-bath.
- B. Medicated.
  - (1) Sea-bathing.
  - (2) Common saline bath. Artificial sea-water made by dissolving bay-salt in water (1 lb. of salt in 30 gals. of water).
  - (3) Carbonic acid and saline.
  - (4) Acid bath.
  - (5) Alkaline bath.
  - (6) Sulphurated bath.
  - (7) Mustard bath.
  - (8) Pine bath (Fichtennadelbad).

II. VAPOUR.	A. Aqueous.	(1) Simple.	Russian.
			Simple vapour.
		(2) Medicated.	Vinegar.
	B. Volatilised drugs, e.g. Calomel.		
III. AIR. . .	Turkish bath.		

Cold Bath.—The effect of a bath depends very much upon its temperature.

In a cold bath, the temperature of the water is at or below 70° F.

The **first** effect of immersion in a cold bath is contraction of the vessels of the skin, accompanied by a feeling of chilliness and perhaps even of shivering. When the water reaches the level of the chest, the respiratory centre becomes reflexly affected, and the respiration becomes gasping.

After a few minutes the cutaneous vessels begin to relax, and the blood returning to the surface warms it. If the person now comes out of the bath, dries quickly and rubs vigorously, the brisk circulation in the skin gives rise to a pleasant feeling of warmth.

The feeling of warmth, or at least of lessened coldness, will occur even if the bath be continued, but the increased circulation in the skin allows the blood to be much more rapidly cooled, and thus the temperature of the body is much more quickly reduced. When the blood which has been thus cooled in the skin returns to the nerve-centres, it appears to stimulate the vaso-motor centre and produce a second contraction of the cutaneous vessels, accompanied by a greater and more persistent chilliness than before.

The **object** of cold baths is usually :—1st, either to have a **tonic** and bracing influence on the body; or 2ndly, to **abstract heat** from the body in cases of fever.

As a **tonic** the cold bath is often very efficacious, and not only gives a feeling of strength and comfort, but tends to prevent those who take it from catching cold so readily as they might otherwise do. The vessels of the skin are, as has already been mentioned, the regulators of temperature, and contract when they are exposed to cold : thus protecting the internal organs from its chilling influence. But Rosenthal has found that when animals are kept for a long time in a warm chamber, their vessels lose to a great extent their contractile power, and thus the animal becomes much more readily chilled when exposed to cold. Cold baths, by training, as it were, the cutaneous vessels to contract, tend to protect the organism from the injurious effects of accidental exposure. Besides this, however, the stimulation to the circulation which comes as an after-effect, tends to increase both the tissue-change in the body, and the excretion of waste-substances from it. In consequence of this, cold bathing is usually followed by an

increased appetite, so that the most favourable conditions for the nutrition of the body are supplied by cold baths, viz. increased supply of food, increased tissue-change, increased excretion of waste.

Cold baths may therefore be looked upon as a most **powerful tonic.**

But while cold baths are of great use to those with whom they agree, they **may be productive of great harm** when they are indiscreetly used. As a general rule it may be said that when they cause much discomfort during the bath, and especially if they cause chilliness afterwards, not removed by brisk friction, they do harm rather than good. This is more especially the case with children and with persons of feeble circulation.

Rosenthal's experiments, already quoted, show us that there is a scientific basis for the popular notion of '**hardening**' by exposure. But this process may be carried much too far, and instead of getting excitement of the circulation with all its attendant advantages, the effect of the bath may be to lower the temperature, depress the circulation, and greatly injure the nutrition. The **risk** of such injury may be much **diminished** by proper attention to the mode of giving the bath. In children or delicate persons it is better, as a rule, to avoid immersing the whole body, and especially to avoid putting the feet in cold water at the same time as the body. The best way is to let the person sit down in a sitz-bath with the feet out and quickly to dash the water over the face, chest, back, and arms. Then a large bath sheet is to be thrown around the body so as completely to envelope it, and to prevent its being chilled during the process of drying. For during the exposure of the body while the surface is still wet, the chilling process is going on by evaporation during summer, and by conduction by the cold air in winter. This may be seen markedly in persons of a feeble circulation who rise from the bath with a feeling of slight glow, but lose it completely and begin to feel chilly, if the process of drying is delayed. Instead of a bath sheet, a dressing-gown made of towelling may be used. For very delicate persons the water of the bath should be rendered tepid by the addition of a little hot water, and the face may not be sponged until after the rest of the body has been dried and the clothes put on. In winter the temperature of the room must not be too low; it is best, therefore, for delicate persons to take a slightly tepid bath before a fire. Tolerance to cold is moreover often established by gradually reducing the temperature of the water in successive baths, care being taken that no feeling of chilliness supervenes.

Sometimes the vigorous use of a flesh-brush over the chest tends to assist the reaction, and, if practicable, a short though brisk walk is advisable just after the bath. It must not, however,

be long, as otherwise exhaustion might set in, and the appetite instead of being increased would be diminished.

Besides the tonic action which cold baths exert on the circulation and on the body generally, they appear to have a beneficial action in certain disturbances of the respiration.

The respiratory centre (p. 241) may be strongly affected reflexly by cold applied to the surface of the chest, as is shown by the gasping breathing, or inspiratory tetanus, observed when the cold water reaches the chest on walking slowly into it. In children suffering from broncho-pneumonia the severe attacks of dyspnœa which sometimes occur are relieved by a momentary immersion in water at a temperature of 60° F.

Cold sponging, as recommended by Ringer in his excellent work on Therapeutics, is exceedingly useful in laryngismus stridulus. It should be used two or three times a day whatever be the weather. If the child be hoarse, it should not be allowed to go out, but if there is no hoarseness, the fresh air, even if cold, will be advantageous. To arrest a paroxysm cold water should be dashed over the child.

Ringer also recommends it for a catch in the breath occurring in young children during the night, awaking them from sleep.

By abstracting heat, cold baths are useful in **fever** in several ways. By reducing the temperature they tend to lessen the amount of **tissue-change** which is already excessive, and they thus tend to husband the patient's strength, as well as to reduce the alterations of the tissues, such as fatty degeneration of the heart, which occur in consequence of a high temperature. By lessening the temperature also, they diminish the rapidity of the pulse, and by thus prolonging the cardiac diastole give more opportunity for the nutrition of the muscular walls of the heart.

A high temperature, if it is remittent, is better supported than a lower temperature which is continuous, and therefore Liebermeister, to whom we in a great measure owe the recent introduction of cold baths as a therapeutic measure, uses them with the object of increasing and prolonging the remissions in temperature which usually occur spontaneously in febrile diseases—producing a condition of 'relative apyrexia.'

There are several ways of employing cold baths to reduce temperature. One is that of **cold affusion,** in which the patient is put into a tub and four or five gallons of cold water thrown over him. Another is to place the patient in a **bath** at about 90° F. and **gradually reduce** the **temperature,** by the addition of cold water, to 80°, 70°, or even 60° F. The patient is kept in this from ten to twenty minutes, according to his strength and the height of the temperature. As the temperature continues to fall for some time after the removal of the patient from the water, the bath should not be continued so long as to lower it to

the full extent required while he is in the bath, lest collapse occur afterwards.

Instead of the bath being gradually cooled down, it may be used at once at a temperature between 60° and 90° according to the condition of the patient, and if the temperature be very high, the water must be cooled still more by means of ice, and its action aided by ice given by the mouth and rubbed or laid upon the surface of the body. This treatment may be adopted even although pneumonia be present, if the patient's life is threatened by an excessive rise in temperature. When the temperature rises again the bath should be repeated.

Cold Pack.—The pack is a less efficient means of abstracting heat from the body, but it is useful in causing a different distribution of blood in the body. It is therefore sometimes very useful in lessening delirium and producing quietness and sleep. In employing it, a wet sheet is wrung well out of cold water and wrapped tightly around the patient; over this are wrapped one to three blankets. A little heat is abstracted at first by the cold of the sheet, but this is very little, and indeed it is asserted by some that cold packs, instead of abstracting heat, prevent its escape. The skin soon becomes warm, and frequently profuse perspiration is produced. A certain amount of heat is lost, though perhaps not very much, by the evaporation through the blankets. It is probable, however, that the production of heat is to a certain extent lessened, at least in restless patients, by their movements being mechanically restrained by the sheet, and also by the blood being withdrawn from the internal organs and muscles to the skin. As the pack restrains the movements in a most complete way and with a force against which it is in vain to struggle, while at the same time it is comfortable and soothing, it frequently induces sleep when narcotics have been useless.

Cold sponging is sometimes a very useful means of abstracting heat in cases of fever, where the patient is weak and the temperature, though perhaps not going above 104° or 105° F., tends rapidly to regain its former height after cooling, and where it seems inadvisable to subject the patient to the frequent movement in and out of bed required in cold baths. The loss of heat consequent on cold sponging is due partly to the application of the cold water, but it is due chiefly to the evaporation which takes place from the surface of the body. Consequently sponging with tepid or even with hot water will also reduce temperature.

Cold Douches.[1]—In this form of bath a stream of water having considerable force is directed against a part of the body.

[1] For a short and concise account of the various appliances used in hydrotherapeutics, *vide* Paper on 'Rational Hydro-therapeutics,' by G. L. Pardington, M.D., *Practitioner*, Jan. 1884.

The stream may either be unbroken, and to this the name douche is usually restricted, or it may be broken up by delivery through a rose into a number of minute streams, so as to form a shower or rain bath. If the douche is large (one or two inches in diameter) it causes a great amount of shock and sometimes does much harm. Usually a stream of a quarter of an inch in diameter is quite sufficient for all purposes. Douches are chiefly applied to the spine, spleen, liver, joints, anus, and vagina. The **spinal douche** usually consists of a single stream, and may either be allowed to fall vertically upon the spine, the body being more or less inclined, or it may be delivered from a horizontal pipe with the body in an upright position. It is useful as a stimulant in melancholia, cerebral anæmia, and general debility. To avoid too great depression it is better to apply hot and cold water alternately, unless it is used immediately after a hot application such as a spinal pack. Douches to the head are useful in alcoholic coma. Douches to the **liver and spleen** have been found useful in chronic congestion and enlargement of these organs. The douche applied to stiffened **joints** appears sometimes to be of considerable service.

The **ascending douche** is usually delivered through a rose, so as to form a shower, and it is directed against the perinæum while the patient is in a sitting position. It is useful in hæmorrhoids and pruritus ani, and when used at a regular hour daily, first tepid and then cold, it is useful in constipation.

The vaginal douche is used by the patient lying on her back with her knees drawn up and with the pipe in the vagina. It is useful in vaginal leucorrhœa and cervical catarrh, and in chronic subinvolution and hyperplasia the hot douche at 105°, F. to 110° F. twice a day for several minutes is of much service.

Local Application of Cold.

Sitz-bath.—When a person sits down in a cold sitz-bath, or when he sits down in an empty bath and cold water is poured into it, until it covers the hips, the vessels of the parts exposed to the cold contract, and the blood is consequently driven into other parts of the body. It would appear, however, that not only do the vessels of the skin contract, but also that contraction of the intestinal vessels occurs reflexly through the splanchnic nerves: so that in consequence there is a feeling of warmth and fulness in the head, an increase in the volume of the arm, as measured by the plethysmograph, and a rise of temperature in the axilla.

A cold sitz-bath, when applied only from one to five minutes and followed by a brisk rubbing, tends to increase the amount of blood in the abdominal organs, to quicken the circu-

[1] Pardington, *op. cit.*

lation in the liver and spleen, and to augment the activity of the movements of the intestine and bladder. It may therefore be used with advantage in constipation and in disorders of the bladder depending on weakness, such as either difficulty in expelling the urine or difficulty in retaining it.

In pregnancy, cold sitz-baths are sometimes useful, giving a feeling of comfort and strength, and lessening the sensations of dragging in the abdomen.

Where any tendency to premature expulsion of the fœtus exists they should be avoided, as the increased circulation which they cause in the pelvic organs might lead to abortion.

When cold sitz-baths are continued for a long time, as from ten to thirty minutes, at a temperature from 8° to 15° C., the contraction of the abdominal vessels appears to be more permanent, and thus they may be employed for the purpose of lessening congestion in the intestine, and may be used with advantage in cases of obstinate diarrhœa and congestive enlargement of the liver and spleen.

The effect of a prolonged sitz-bath in lessening congestion of the abdominal organs is greatly increased if it be preceded by a wash-down, with brisk friction, so that the blood may be attracted to the other parts of the surface as well as driven out of the abdomen by contraction of the intestinal vessels.

Cold Foot-bath.—Coldness of the feet not only causes discomfort to the person, but if it occurs at night, it may prevent sleep. Putting them in hot water may warm them temporarily, but will not do so permanently, and a much better way is to put them in cold water, rub them briskly while in it, and then dry them thoroughly with a soft towel, giving them a rub afterwards with a rough bath-towel.

Cold foot-baths are to be avoided during the menstrual period, as they have a very great power indeed to check menstruation and frequently bring on amenorrhœa. Their power to check the menstrual flow is popularly known, and sometimes great harm is occasioned by young women using them to check menstruation, in order that they may be able to attend some party of pleasure.

Cold Compresses.—By the application of cold over the course of an artery, it can be made to contract, and the amount of blood to the district which it supplies may consequently be diminished. This is shown by the accompanying curve taken by Winternitz from the radial artery (Fig. 156).

The first half of the curve (*A*) was taken before anything had been applied to the arm. The instrument being allowed to remain, ice was next applied to the arm, and the second half of the curve (*B*) shows the contraction which it had produced in the artery.

When the cold application is allowed to remain for a while,

it gradually acquires the temperature of the body, and if evaporation be prevented, it comes to have the same effect as warmth,

FIG. 156.—Tracings from the radial artery at the wrist: *A* before and *B* after the application of a cloth dipped in cold water round the arm. (After Winternitz.)

but if constantly renewed, the contraction of the artery may be kept up. A similar contraction to that just noticed in the vessels of the arm may be produced in the vessels of the head by cold applications around the neck. This is shown by the fall of temperature in the auditory meatus. Cold may be applied to the neck either by a bag containing ice, or by an india-rubber bag, or coils of tubing, through which cold water may be kept constantly flowing.

As a very large proportion of the whole blood in the body flows through the carotids, the application of cold to the neck may act as a general antipyretic. The accurate application of ice-bags to the neck so as to cover the supra-clavicular regions also, and thus to cool the blood in the subclavians, has been recommended in fever, to reduce the temperature generally. In tonsillitis cold to the neck is useful, for its local action.[1]

Cold to the head is frequently applied in delirium, meningitis, and severe cephalalgia. It may be applied either by a bag containing cold water or ice, or still more conveniently by a cap consisting of india-rubber tubing through which water constantly flows.

A continuous stream of water through an ordinary water-bed reduces the temperature slightly and thus relieves the symptoms in prolonged fever.

Warm Baths.

Tepid Baths.—These baths range from 85° F. to 65° F. or 29·4° C. to 18·3° C. They are chiefly used for cleansing purposes, and at the lower margin of about 65° F. they may be used for a somewhat tonic action in persons of feeble circulation (p. 461).

Warm Baths.—These range from 97° F. to 85° F., or 36·1° C. to 29·4° C. When the water is above these temperatures it forms a hot bath. The warm water softens the epidermis, and is thus of much use in chronic skin-diseases. It dilates the vessels of the surface of the body, and thus tends to

[1] Stephan, *Allg. med. Central-Ztg.*, No. 87, 1884.

lessen any internal congestion. At the same time it tends to induce perspiration. On this account the warm bath is useful in lessening pain depending on congestion of internal organs and in preventing congestion from going on to inflammation. It is therefore very serviceable when there is a threatening of bronchitis, or gastro-intestinal catarrh, colic, &c. It tends to reduce the temperature both by dilating the peripheral vessels and inducing perspiration, and is therefore useful in febrile conditions. By withdrawing blood from the brain it tends to induce sleep.

Hot Baths.—These range from 97° F., or 36·1° C., upwards. A much higher temperature than can be endured at first can be borne if the temperature be gradually raised by the gradual addition of hot water to the bath while the body is immersed, and the bath may thus be raised as high as 110° F. Hot baths not only prevent loss of heat from the surface, but if above the temperature of the blood, actually impart heat to the body. The consequence of this is that the temperature of the body rises very rapidly, and therefore the respiration and pulse both become very quick. The peripheral vessels become still more dilated than in the warm bath, and the blood pours so rapidly through them that, in spite of the quick and powerful action of the heart, there may be a tendency to syncope when the head is raised. After remaining in such a bath from ten to twenty minutes, the patient must be carefully lifted out so as to avoid any risk of syncope, and should be wrapped in warm, dry blankets. The hot bath is a still more powerful agent than the warm bath in producing sweating, and is employed in cases of dropsy.

Hot Foot-bath.—A hot foot-bath has a general effect that can hardly be explained by the simple dilatation of the vessels in the feet and consequent derivation of blood to them. It seems, indeed, to exert some reflex action on other parts of the body and causes a general feeling of warmth. It is very useful as an adjunct to vascular stimulants in relieving congestion and preventing inflammation, as in threatened catarrh, bronchitis, &c. When the feet are put into a hot bath, we find that the femoral arteries become much dilated and pulsate much more vigorously than they did before. It is not improbable that this dilatation extends beyond the femoral to the iliac arteries, and that the supply of blood is increased in the pelvic organs as well as in the feet. In cases of amenorrhœa, especially where it has been brought on by exposure to cold, hot foot-baths tend to restore the menstrual flow. They should be begun four or five nights before the period is expected, and continued during the time it ought to last. Their efficacy may be increased by the addition of a little mustard.

Hot Sitz-baths.—These have a still greater tendency than hot foot-baths to increase the circulation in the pelvic organs,

and they may be used either alone or with mustard in the manner just described in cases of amenorrhœa.

Poultices.—Poultices are simply a means of applying heat and moisture to a limited portion of the surface of the body. Their mode of action has already been discussed (p. 342). They consist essentially of some farinaceous substance made into a paste with hot water, and the most common substances used as bases are linseed meal, bread, bran, oatmeal or starch. In all cases, not only should the water with which the poultice is made be **perfectly boiling**, but the bowl in which it is to be mixed, the spoon with which it is to be stirred, and the tow or flannel in which it is to be laid, should all be as hot as possible. By adding the linseed meal to the water and constantly stirring, there is less chance of the poultice being knotty than if the water were added to the meal. If the poultice is intended to be applied to a wound, sore, boil, or carbuncle, it should be spread upon a piece of flannel or tow and applied directly to the skin, because the softening action of the water and oil it contains on the dermal tissues is required as well as the warmth. But where

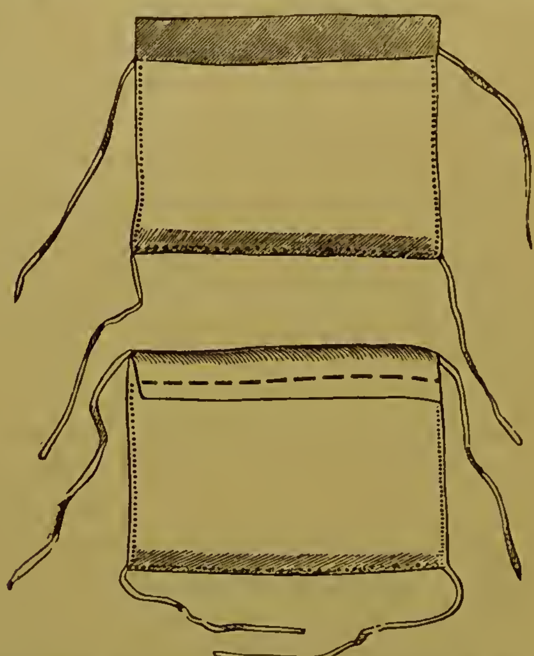

FIG. 157.—The upper figure represents the bag empty; the lower one the bag filled and sewn up.

the poultice is used to relieve pain, congestion, or inflammation of the internal organs, as in pleurisy, pneumonia, or colic—intestinal, biliary, or renal, it ought not to be applied directly to the skin, but should be separated from it by something which conducts heat badly, such as flannel. The reason for this is that it is impossible to apply a very hot poultice directly to the skin on account of the pain it causes, whereas if a substance which conducts heat badly be interposed, the poultice can be applied boiling hot, the heat gradually passes through without becoming inconveniently great, and is retained for a much longer time.

In order to accomplish this, a flannel bag should be prepared, a convenient size being twelve inches by eight; this should be closed at three edges and open at the fourth; one side of it should be about one inch or one inch and a half longer than the other, as represented in the diagram (Fig. 157), and it is convenient also to have four tapes attached at the points which form the corners when the bag is closed, in order to keep the poultice in position. Besides this, another strip of flannel should be prepared of the same breadth as the length of the bag, and long enough to wrap round it once or oftener. Crushed linseed, bowl, and spoon should then be got together, and the spoon and bowl thoroughly heated by means of boiling water; the poultice should then be made with perfectly boiling water, and rather soft. As soon as it is ready it should be poured into the bag, previously warmed by holding it before the fire; the flap which is formed by the longest side of the bag should now be turned down and fastened in its place by a few long stitches with a needle and thread; it should then be quickly wrapped in the strip of flannel (also previously warmed), and fastened *in situ*, if necessary, by means of the tapes. It may be covered outside with a sheet of cotton wool.

Medicated Baths.

The addition of stimulating substances, such as **salt**, to the water, increases the stimulation to the skin, and the amount of after-reaction.

In **sea-bathing** the stimulating effect of the salt is further increased by the mechanical shock of the waves, and sometimes also by the friction of the fine sand of the beach. Sea-bathing also differs from baths in the fact that muscular exertion is combined with it, either in simply moving about and retaining one's footing, or still more in swimming.

Carbonic Acid Bath.—This is a saline bath, containing two to three per cent. of chloride of sodium, and not more than one per cent. of chloride of calcium, with varying proportions of free carbonic acid up to 3 grammes in the litre. It has been recommended for chronic heart-disease, both functional and organic, and is said to act as a cardiac tonic.[1]

Acid Bath.—This bath is made by mixing eight ounces of nitro-hydrochloric acid with a gallon of water at blood heat (98° F.) This is sometimes used as a foot-bath, but it is better applied as a compress. A flannel roller about a foot wide, and long enough to go twice round the body, should be soaked in the acidulated water, wrung thoroughly out, and rolled round the region of the liver; a piece of oil-silk, large enough to cover it

[1] Aug. Schott, *Berl. klin. Wochensch.*, No. 33, 1885.

completely and leave a little margin over, should then be put over it. It may be worn for several days, being renewed every night, and it is chiefly useful in chronic disease of the liver.[1]

Alkaline Bath.—This is made by adding crystallised carbonate of sodium to water in the proportion of about one drachm to each gallon. It is chiefly used in chronic skin-diseases.

Sulphurated Bath.—This may be made by dissolving sulphurated potash in water, about half a drachm to the gallon, or, in imitation of Barège waters, may be made by mixing sodium sulphide, sodium carbonate, and sodium chloride in the proportion of twenty grains of each to the gallon. These are chiefly useful in chronic scaly skin-diseases, and in rheumatism. Much more benefit is usually obtained by a visit to sulphur springs, such as those of Aix-les-Bains, Aix-la-Chapelle, Barège, Harrogate, or Strathpeffer, than from the use of sulphur baths at home.

Mustard Bath.—This is made by adding mustard to water in the proportion of about half a drachm to a drachm and a quarter per gallon. It is a powerful stimulant, but must not be applied too long. It must be remembered that, while slight stimuli to the skin increase the frequency and energy of the cardiac contractions and the rapidity of the circulation, and raise the temperature, severe irritation of the skin lessens the frequency of the pulse and the rapidity of the circulation, dilates the vessels and lowers the temperature.[2] The patient should never be allowed to remain more than ten minutes in the bath, and should be at once removed as soon as he feels either burning of the skin or icy coldness. Mustard baths are generally used in order to quicken the appearance of the eruption in the exanthemata.

Pine Bath.—This is made by adding a decoction of the shoots of pines to water, but it is more convenient to use the oleum pini sylvestris in the proportion of one minim to the gallon. These baths are used in rheumatism, gout, paralysis, scrofula, and skin-diseases.

Vapour Baths.

In these the body is exposed to steam instead of being immersed in hot water. The effect is much the same as that of the hot bath. The so-called Russian bath consists of a room filled with steam and provided with benches at various levels. The higher the level the greater is the heat, and usually, excepting on the lower benches, it is only possible to breathe with any

[1] Squire's *Companion to the British Pharmacopœia*, 13th ed.

[2] Naumann, *Prager med. Jahrschr.*, 1863, i. p. 1, and 1867, i. p. 133; Heidenhain, *Pflüger's Archiv*, Bd. iii. p. 504, and Bd. v. p. 77; Riegel, *Pflüger's Archiv*, Bd. iv. p. 350.

comfort by holding a sponge dipped in cold water before the nose. From this room the bather goes to another where he is drenched with cold water by a douche, and is then quickly dried, and allowed to rest for some time before dressing. These baths are chiefly used in chronic rheumatism. They are liable to the same objections as the hot bath, and to a still greater extent, for the inhalation of the hot steam produces greater difficulty of breathing, greater acceleration of the pulse, and greater tendency to syncope. Vapour baths, in which the body only is exposed to the action of the steam, and the head is left out are much better. They are usually applied either by means of a kind of box in which the body of the bather is enclosed while the head remains outside, or else by introducing steam under the bedclothes, which are supported by a kind of cradle, while the bedclothes are tucked tightly round the patient's neck to prevent the escape of the vapour. The latter plan is very useful in cases of dropsy and uræmia, as it induces a copious perspiration and does not exhaust the patient nearly so much as a hot bath. In cases of acute rheumatism a vapour bath of vinegar has been recommended.

Calomel Fumigation.—This is used as a means of inducing the general action of mercury. The patient is seated naked on a wickerwork chair, underneath which is put a stand holding a shallow cup containing 20 to 30 grains of calomel. The calomel is volatilised by means of a spirit lamp, and a blanket or waterproof sheet being thrown round the patient so as completely to envelope himself, his chair, and the fumigating apparatus, the calomel fumes become condensed upon his skin in a fine state of division. It is absorbed with considerable rapidity, probably from becoming mixed with the sebaceous secretion from the skin, and the general action of mercury is quickly induced.

Air Baths.

Turkish Bath.—The Turkish bath usually consists of three rooms, although frequently there are more. The temperature of the first, or dressing-room, is moderate, that of the second is higher, and that of the third is higher still. In the first room, the bather, after undressing, winds one towel round his loins, and a second round his head in the form of a turban. If he has any tendency to cerebral congestion, the second one may be wet. He then passes into the second room, where he usually waits a short time before passing into the third room. Some people, however, go directly into the third room. In both the second and third rooms the bathers partake freely of cold water. A few minutes' stay in the warmest room is usually sufficient to make the bather perspire freely, and he then returns to the second or

cooler room, where he may remain half an hour or more, according to circumstances. He may then be shampooed, the surface of the body being rubbed, the muscles kneaded, and the smaller joints extended. He is next washed with a lather of soap, and sluiced with basins of tepid or warm water. For some people it is most agreeable after this to be simply wrapped in warm towels and allowed to repose in the dressing-room. Others prefer to finish up with a cold douche before proceeding to the dressing-room. Here they remain resting for a considerable time before they again dress. Turkish baths are exceedingly useful in chronic rheumatism and gout, and in persons suffering from the effects of malaria. The chief objection to the Turkish bath is the length of time that it takes. In some persons it has a weakening effect, but in many others it has none. The chief precautions are not to stay too long in the hot room, and to leave it at once if giddiness or a feeling of tightness in the head comes on. If the skin perspires with difficulty, the necessity for caution in entering the hot room becomes still greater, and it is advisable rather to spend a longer time in the second room, and drink freely of water before entering the hotter room, if, indeed, this be entered at all on the first few times of taking the bath. Persons who suffer from a feeling of exhaustion after a Turkish bath should not take a cold douche nor a plunge into water after perspiring, but should simply allow themselves to cool very gradually, and should take some stimulant, such as coffee or beef-tea, while doing so. Persons who suffer from malaria also should spend a good while in the second room before attempting to enter the third, as the sudden application of heat to the skin and lungs seems to irritate the vaso-motor centres and cause chilliness, or even shivering.

Friction and Inunction.

Friction of the skin causes first a temporary contraction of the vessels, followed by a more or less permanent dilatation, so that the skin continues red for a length of time after the irritation has ceased. This redness is accompanied by a warm glow from the increased circulation in the skin, and friction is therefore useful as an adjunct to cold baths. Besides this, friction along the extremities in an upward direction tends to aid the flow of lymph, and thus to remove the products of waste from the muscles.

The fascia covering a muscle forms a pumping apparatus for removing waste-products from the muscles (Fig. 158). It consists of two layers, *a b* and *e f*, and between these are lymph spaces, some of which, *x*, are seen in transverse, and others, which appear black from the injection with which they are filled, are seen in longitudinal section. Each time the muscle contracts, it becomes

thicker, presses the two layers of fascia together, and drives the lymph from the spaces onwards into the lymphatics. Each time the muscle relaxes, the layers of fascia tend to separate, and

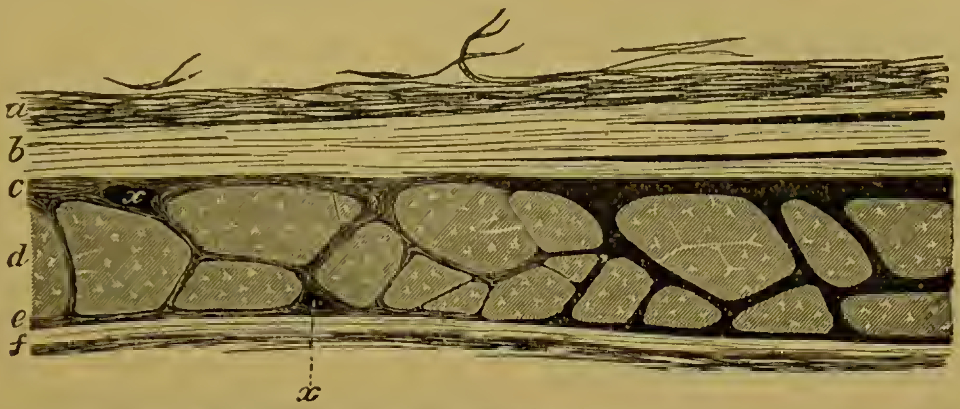

FIG. 158.—Injected lymph-spaces from the fascia lata of a dog. The injected lymph-spaces are black in the figure. (After Ludwig and Schweigger-Seidel.)

lymph from the muscle, carrying with it the waste-products, fills the spaces between the layers. The action of the muscle itself thus tends to remove the waste-products which give rise to fatigue (*vide* Massage, p. 131), but after over-exertion their removal may be greatly aided by gentle but firm upward friction, which will have a similar action on the fascia to the alternate compression and separation of its two layers, caused by the action of the muscle itself.

Gentle firm friction thus lessens or may even remove entirely the feeling of **fatigue** and weight in the extremities after exertion. When applied to the nape of the neck, or along the spine, it is sometimes useful in headache, in nervous irritability, and in sleeplessness.

When applied between the shoulders in persons suffering from flatulence, it appears to aid the expulsion of gas from the stomach.

The effect of friction as a **counter-irritant** is greatly increased by the use of stimulating liniments. These are applied by pouring a little into the hollow of the hand and then rubbing it over the surface of the body, or else by soaking a piece of flannel in the liniment and rubbing the skin with it. Linimentum ammoniæ applied thus to the chest is useful in the bronchitis of children; and linimentum camphoræ compositum, B.P., or linimentum terebinthinæ may be used in a similar way for adults.

In chronic inflammation of joints, liniments may be applied in a similar way. Sometimes it may be advisable also in such cases to swathe the joint in a piece of flannel or lint, soaked in the liniment so as to procure more continuous application.

Inunction.—Metallic salts are very slightly, if at all, absorbed from the skin when applied to it in watery solution, and wiped off without being allowed to dry. But when applied in

the form of ointments a considerable absorption takes place, especially if lanolin be used as a basis. Advantage is taken of this, in order to obtain the *general* action of mercury without its *local* effect on the intestinal canal. For this purpose mercurial ointment is rubbed on the skin, and especially on those parts where the epidermis is thin, as under the axillæ and on the inside of the thighs.

Absorption also takes place, however, through the skin of the hands, and if the ointment is not rubbed on by the patient himself, but by another person, in whom the action of mercury is undesirable, it has been recommended that the latter should cover his hands with a piece of bladder thoroughly well oiled in order to prevent absorption.

In children, instead of applying the mercurial ointment by inunction, it is customary to smear the ointment on a piece of flannel, and to keep it applied to the abdomen of the child by means of a bandage.

Endermic Application of Drugs.

This method consists in applying the drug to the skin previously denuded of its epidermis or epithelial layer by blistering. The drug may be applied in the form of powder, solution, ointment, liniment, or plaster, but most frequently in the form of powder. The drug is more readily absorbed when applied in this manner than when applied over the epidermis. Cantharides may be used for the purpose of raising a blister, but a more convenient method is to fill a thimble with cotton-wool or lint soaked in the strongest liquor ammoniæ, apply it to the spot and keep it on for five minutes. If the cuticle has not then risen in a blister apply a poultice until it rises. Cut off the cuticle, place the powder on the denuded surface, and cover it with a piece of oil-silk fixed in position by two pieces of strapping crossed over it. This method was chiefly employed for the local application of morphine. It has now been almost entirely superseded by the hypodermic method, but may still be occasionally employed in cases where it is advisable to combine the counter-irritant action of the blister with the local sedative effect of the morphine.

Hypodermic Administration of Drugs.

This method, the introduction of which we owe to Dr. Alexander Wood of Edinburgh, possesses great advantages.

It consists in the injection of a solution of a remedy under the skin. Absorption takes place from the subcutaneous cellular tissue rapidly, and it is much less likely to be modified by altered conditions of the organism than absorption from the stomach

and intestine. For in the intestinal canal there is not only the condition of the circulation to be taken into consideration, but the fulness or emptiness of the stomach and intestine, the condition of their epithelial covering and of their nervous supply, and the state of the liver. These conditions may not only delay but entirely prevent absorption.

The advantages of the hypodermic method, therefore, are 1st, certainty of effect, and 2nd, rapidity of action.

As absorption of a drug takes place so much more rapidly from the subcutaneous cellular tissue than from the stomach, a less quantity is excreted during the process of absorption, and consequently a smaller quantity of the drug is required (p. 38 *et seq.*).

But absorption does not take place with equal rapidity from all parts of the intercellular tissue. The vascularity of this tissue, and the rate of absorption from it, are greater on the temples and breast than on the back, and greater on the inner than on the outer surface of the arms and legs.

As the liquids used for hypodermic injection are usually concentrated solutions of powerful poisons, it is important that neither more nor less than the quantity previously determined upon should be administered. The syringe consists of two parts

FIG. 159.—Syringe for hypodermic injection.

(Fig. 159), a glass barrel in which a piston plays airtight, and a hollow needle which fits tightly on to the end of the syringe either with or without a screw. The bore of the needle being very fine it is apt to get choked by rust, or by crystals of the substance last employed for injection forming within it, and rendering it impermeable and useless. In order to avoid this it should be carefully washed with water each time it is used, and a small piece of thin wire kept constantly in it during the intervals of use, or, better still, a little oil drawn into the bore of the needle. When the syringe has not been used for some time, the packing of the piston is apt to shrink, so that it will no longer either suck in fluid or drive it out of the barrel efficiently. This may often be remedied to a great extent by soaking the syringe for a short time in warm water and driving the piston up and down in it. If this is insufficient the piston may be taken out, and sufficient thread wound round it to make it work. Care must be taken also that the needle fits tightly on the syringe, and that no leakage takes place at the junction. The liquid to be injected should contain no solid particles which may obstruct the needle, and if any such should be present, the fluid may be filtered through clean blotting-paper.

The exact quantity required, and no more, should then be drawn up into the syringe and injected. Some syringes have a small screw upon the piston, so as to stop its movement at any required point. With such a syringe the barrel may be filled quite full of the solution, and the required quantity injected by forcing the piston down until it is stopped by the screw. The advantage of this arrangement is that if any leakage should occur, the screw may be moved further up, and an additional quantity of solution injected without the necessity of withdrawing and reintroducing the needle under the skin. If all proper precautions be taken, however, the necessity for such a procedure will rarely arise.

Convenient places for injection are the outside of the arm near the deltoid, the fore-arms, or the thighs. In order to avoid the risk of introducing the needle into a vein, the injection should not be made over a vein visible through the skin. The skin should be pinched up between the finger and thumb, the needle pushed directly through it, and then passed onwards a little way obliquely in the subcutaneous cellular tissue.

Objections to Hypodermic Injections.—The chief objections are, (1) the pain caused at the time by the introduction of the needle, or by the drug itself after its injection, (2) the inflammation which either the needle or the drug may give rise to subsequently, (3) the scars which may be left by the frequent repetition of the injection, (4) the danger of communicating a specific or contagious disease, (5) the danger of injecting the drug directly into a vein, and thus producing a dangerous or fatal effect from the too rapid entrance of the drug into the circulation. With a little care these untoward results may be almost entirely avoided. If the needle is well sharpened the pain of introducing it is very slight, and may be still further lessened by making the patient take several deep breaths in rapid succession before the injection is made. If the patient is excessively sensitive, partial or complete anæsthesia of the part may be produced by cold or by carbolic acid (p. 204).

The solutions should always be perfectly free from solid particles and should be as neutral and bland as possible. Metallic salts have their irritating properties diminished or removed when combined with albumen or with an alkaline citrate or tartrate so as to form double salts.

By washing the syringe and needle thoroughly out with carbolic acid, the danger of conveying any specific or contagious disease is rendered very slight, and it may be completely avoided by heating all parts of the syringe in a spirit-lamp before using them. The syringe employed by Koch in his experiments on the effects of micro-organisms in producing disease (Fig. 159) is admirably adapted for this purpose, as all parts of it can be readily heated, and the padding upon the piston, which is more

likely to retain infective matter than any other part of the syringe, can be renewed each time that the instrument is employed. In order to prevent pain or inflammation being caused by the solution injected, care should be taken that its reaction is as nearly as possible neutral, and that the quantity should not be great. The smart which follows the injection is lessened by rubbing the finger gently over the part so as to distribute the fluid in the subcutaneous tissue. If it is necessary to employ such large quantities as half a drachm or a drachm, as may be the case with ergot, it is better not to inject the solution under the skin but into the substance of a muscle, such as the gluteus maximus.

Cicatrices are not apt to follow injection if the precautions already mentioned have been taken, and if the injections are not made too frequently at the same point.

Application of Drugs to the Eye

For inflammation of the lids, ointment is smeared between the edges.

Cold water is applied to the conjunctiva for its tonic action, by keeping the eyes open and then dipping the face into a basin of water.

Strong solutions like that of atropine are applied to the conjunctiva by dropping them into the outer canthus of the eye and allowing them to flow over the surface. If such a solution is to be applied frequently, it may be dropped into the inner canthus, and the head held so as to allow it to drop out of the outer canthus; for when the reverse procedure is employed the atropine may pass down the lacrimal duct, and being absorbed may produce its general effect upon the system and cause symptoms of poisoning.

Application of Drugs to the Ear.

Astringent solutions are usually applied to the auditory meatus, by injecting them in a gentle stream by means of a small syringe (Fig. 160).

FIG. 160.—Vulcanite syringe for injecting solutions into the ear.

For the mode of injecting into the middle ear, special treatises on aural surgery must be consulted.

Application of Drugs to the Nose.

Drugs are applied to the nose in the form of powder, which may be taken in the same way as **snuff** by putting a little on the top of the thumb, holding it in front of the nose and strongly inspiring; or the powder may be put on a small piece of card-board in which a pinhole has been made just under the powder, or with a small perforated spoon like that used in Scotland for snuff. Sternutatories may be used in this way, and so may Ferrier's powder for soothing the mucous membrane in cases of commencing catarrh.

Fluids may be applied by **insufflation**, the nose being simply immersed in them and strong inspiration being made.

They may also be applied by the **nasal douche**. This consists simply of a long india-rubber tube to act as a syphon (Fig. 161). The upper end of it is placed in a vessel filled with the

FIG. 161.—Nasal douche.

solution to be applied, and it is prevented from falling out by a hollow lead weight attached to its upper end. At the lower end is a conical nozzle, which completely plugs the nostril. The tube being filled with the fluid by suction so that it commences to act as a syphon, the nozzle is placed in one nostril, and the head is held with the mouth open over a basin. In this position the posterior nares are cut off by the soft palate from the pharynx, and the solution passes up one nostril and not through the other, so that the nasal cavity is washed out and its mucous

membrane acted upon by the solution which is employed. By altering the position of the head, both in insufflation and in washing with the douche, the part of the nose reached by the fluid will be changed. Thus when the head is held much forward, the anterior and upper part of the nose will be chiefly cleansed, when the head is held upright, the posterior and lower, and when the position is intermediate, the middle part of the nose will be most affected.

The nose may also be washed out by using a large syringe (ear) with a piece of india-rubber tubing fitted on to the nozzle. If at the moment of injection the patient be directed to say 'anemone' (or some such word) and expectorate, the injection will come out of the mouth.

Pure water is irritating to sensitive mucous membranes like that of the nose, and so instead of employing pure water it is much better to use a ·5 to 1 per cent. solution of common salt, which is a bland, non-irritating fluid. Such a solution may be made by adding a drachm of common salt to a pint of water.

Fluids may also be applied to the nose in the form of spray, either directed simply into the nostrils, or by means of a catheter perforated with a number of minute holes, and introduced along the floor of the nasal fossæ. The former may be used for applying astringent and deodorising solutions, and the latter for the purpose of washing out the nose and removing hardened secretions.

Application of Drugs to the Larynx.

Solid powders may be applied to the larynx by **insufflation**. The insufflator (Fig. 162) used for this purpose consists of a tube curved at one end, and having at the other a piece of india-rubber tubing or an india-rubber ball, by which a powder may be blown through the tube near this end of the tube. There is a small opening in its side through which the powder may be introduced, and this is afterwards covered by a sliding ring or a piece of india-rubber tubing so as to prevent the powder from escaping. The bent part of the tube is carefully introduced into the mouth so as not to cause retching by touching the tongue or soft palate, and, when the end of it points down over the larynx, the patient is told to take a deep breath. At the moment of inspiration the operator forces the powder out of the tube into the larynx, either by blowing through the india-rubber mouthpiece, or by compressing the india-rubber ball. Morphine applied by this method gives more relief than almost anything else in laryngeal phthisis. About one-sixth of a grain is sufficient, and in order to give it sufficient bulk it may be mixed with either starch or bismuth.

Solutions may be simply applied by means of a sponge firmly tied to a piece of whalebone having the proper curve; as the

patient inspires this is pushed down the larynx. Doubts have been expressed as to whether the sponge does get through the larynx, but I have seen the crico-thyroid membrane projected forwards by the sponge applied in this manner.

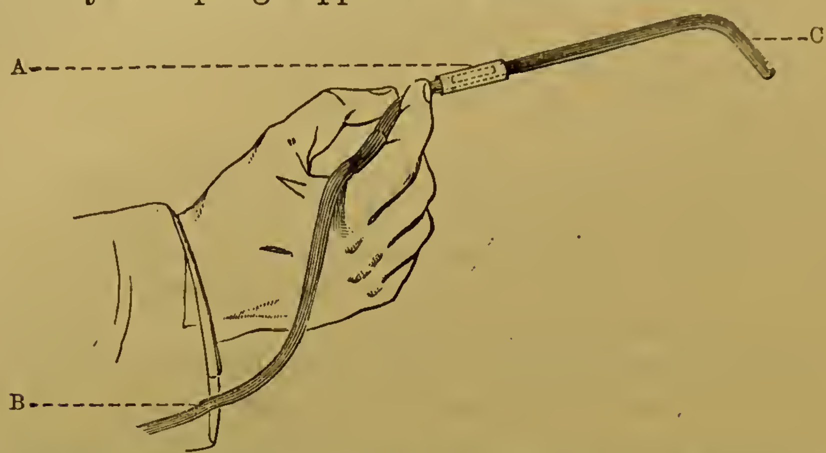

FIG. 162.—Insufflator for applying powders to the larynx. A, piece of india-rubber covering the opening in the insufflator, by which the powder is placed in it. B, india-rubber tube by which the powder is blown out of the insufflator into the larynx. C, curved end of insufflator for introduction into the pharynx.

Nitrate of silver applied in this way gives relief in cases of phthisis, but it is a very rough method, and the application of the solution by means of a brush, with the aid of the laryngoscope, is much to be preferred. When the sponge has not been firmly fixed it has been known to come off and fall into the trachea.

Fluids may be applied by a brush to the larynx, the operator using the brush with one hand and holding the laryngoscopic mirror with the other, while the patient holds his tongue out himself. If the patient is made to take several deep breaths in succession, a slight anæsthetic condition is produced, which renders the operation much more easy.

Caustics are best applied to the larynx by means of a caustic-holder in which the caustic is concealed until it reaches the point of application, when it can be projected by a touch of the finger, and again withdrawn at the wish of the operator.

Solid nitrate of silver may also be applied by heating the end of a partially curved metal rod, then touching the stick of caustic. In this way a uniformly-diffused and minute quantity of the caustic is melted on to the end of the instrument, which is then applied by aid of the mirror.

Liquid may be applied to the larynx in the form of spray, produced either by means of Richardson's apparatus or by a current of steam. The nozzle of the spray-producer may be simply directed towards the pharynx, or the tongue and the cheeks may be protected from the spray by a cylindrical glass speculum.

Application of Drugs to the Lungs.

Inhalations.—**Vapours** employed as inhalations act not only on the bronchial tubes but upon the larynx, pharynx, and nostrils. One of the commonest is that of simple hot water. A jug is filled about half-full of boiling water and the head held over it, the steam being kept in by means of a napkin or towel thrown over the head and around the mouth of the jug. This application often gives great, though temporary, relief in nasal, laryngeal, and bronchial catarrh.

Vapour may be **medicated** by the addition of various substances to it, such as carbolic acid, tincture of benzoin, creasote, or pine oil. But in order to gain the full advantage of the admixture of these substances it is better that the inspired air should not merely play over the surface of the hot water, but be drawn through it, and for this purpose **inhalers** are employed. In these the air is inspired by means of a mouthpiece fitted with a valve. This valve prevents the air from passing into the mouthpiece, so that during inhalation it is sucked through a tube which dips under the water and passes into the mouth laden with the vapour. During expiration it passes readily through the valve just mentioned.

In cases of bronchitis the patient breathes much more easily when the air of the room is kept warm and moist, and this is effected by means of a **bronchitis kettle.** This is simply a tin kettle with a spout about three feet long which projects into the room, so that when the kettle is kept boiling briskly a constant current of steam is driven well out into the room. When this cannot be obtained a substitute may be extemporised by rolling a piece of brown paper into a tube, tying a piece of string around it at intervals so as to keep it in shape, and putting it over the spout of an ordinary kettle. In cases of tracheotomy it is usual to keep the air still warmer and moister by hanging sheets around the bed so as to convert it into a kind of tent, and then conveying the steam from a bronchitis kettle into it by means of an india-rubber tube, or keeping up a constant spray by one of Lister's steam spray producers.

The vapour of the drug itself, without admixture with steam, may in some cases be inhaled (see Vapores, p. 533). Oil of eucalyptus or a solution of thymol in alcohol is thus useful as an antiseptic inhalation in gangrene of the lung and bronchiectasis. Terebene is also used in this way in cases of emphysema and chronic bronchitis. The vapour of pyridine in a room is used in asthma.

Smoke.—The attacks of difficulty of breathing which come on in cases of pure spasmodic asthma, in advanced kidney disease, or in emphysema, are frequently much relieved by inhaling the smoke which issues from burning touch-paper or from powdered

stramonium (*vide* also p. 260). The touch-paper or stramonium may be simply laid on a plate, or may be placed at the bottom of a cup or jug, and the fumes inhaled. Datura is often used in the form of cigarettes made either from the leaves of the datura stramonium or datura tatula.

Application of Drugs to the Digestive Tract.

Mouth and Pharynx.—Weak solutions are applied to the mouth in the form of **washes** with which the mouth is rinsed out. Stronger ones may be **painted** with a camel's-hair brush inside the cheek, lips, gums, tongue or pharynx. Solutions may be applied to the pharynx by painting with a brush; solid substances, as caustics, by **rubbing**. In using caustic, care must be taken that it is firmly attached to the caustic-holder, and, in the case of nitrate of silver, that only a short point is used, as otherwise the caustic may fall off, or the stick of nitrate of silver may break and be swallowed. This is especially necessary in touching the throat in children. In cases of post-nasal or pharyngeal catarrh, solutions such as glycerin of tannin, &c., may be applied to the back of the soft palate and the **posterior** part of the **nares** by means of a camel's-hair brush fixed on a wire which may be bent to any desired angle.

Masticatories.—We sometimes give the patients solid pieces of a drug to chew. These are called masticatories. We use them for their action upon the mouth itself, e.g. pellitory, where we wish to increase the secretion of saliva; or where we not only wish to produce the effect upon the mouth, but the effect of the drug mixed with the saliva upon the stomach and intestines, as in the case of rhubarb.

Gargles.—In gargling, a full breath is taken, the mouth is filled with the liquid which is to be applied to the pharynx, and the head being then thrown back the fluid runs against the pharynx and is partly thrown up against the soft palate by the air which gradually escapes from the lungs. In cases where it is advisable for the fluid to reach the posterior nares, the patient should lie down flat, take a mouthful of the liquid, draw out the tongue as far as possible with a handkerchief, and gargle while in that position. By throwing the head suddenly forward the liquid may be brought through the nose. This is useful both as a method of applying the liquid more thoroughly to the pharynx and as a training preparatory to rhinoscopic examination.[1]

Stomach.—Drugs are applied to the stomach in the form of solutions or draughts, pills, powders, or boluses, &c., which are swallowed.

Powders may be very conveniently given in wafers. A thin wafer is moistened with water, and the powder being introduced,

[1] Rumbold, *Chicago Med. Journ.*, August 1877, p. 113.

is folded up in it and swallowed. Another most convenient vehicle is oatmeal porridge, a little of which is put upon a spoon, and, a depression being made in it with the finger, the powder is put into it and covered over with porridge. The porridge should fill the front half of the spoon, and the back part should be filled with milk, which helps the child to swallow more easily. Powders are sometimes given to children in jelly, but this is too soft, and so also is the paste made of bread and milk, although this may be used when porridge cannot be readily obtained. Pills may be simply swallowed with water, or taken in jelly, but some people are unable to take them without choking, and children especially have much difficulty in swallowing them. This difficulty is readily got over by dividing the pill into four or more parts, and taking each part in a little oatmeal porridge. Custard puddings, or puddings made of corn-flour or arrowroot, may be used instead of porridge, but are hardly so good.

Stomach-pump.—In cases where the patient is unable to swallow from paralysis of the pharynx, constriction of the œsophagus, or narcotic poisoning, the stomach-pump may be used. This consists of a large, double-acting syringe with a flexible tube attached. In using it care must be taken [1] (1) to have the tube well softened in hot water; (2) to keep its end directed towards the pharynx, and not bent too much forward, lest it enter the larynx; (3) not to use violence in introducing the tube, lest it should be driven into the mediastinum, or even through the walls of the stomach itself, into the peritoneal cavity; (4) not to use violence in working the syringe, lest the mucous membrane of the stomach should be drawn into the lower orifice of the tube and injured.

In place of the stomach-pump the **gastric syphon** may sometimes be advantageously employed, especially for feeding. It consists of a piece of thick-walled, soft, and flexible india-rubber tubing. It is so soft and flexible that it can hardly by any possibility injure the œsophagus or stomach, and yet it is sufficiently firm to pass down without much difficulty. After it is in, an ordinary funnel is attached to the projecting end, and water, beef-tea, or whatever substance one wishes to introduce into the stomach, is simply poured in, the funnel being kept at, or above, the level of the patient's mouth. When it is desired to empty the stomach water is poured in, in the manner just described, the tube being pinched, and then the outer end of the funnel is held down as low as possible—the syphon action is thus reversed, and the fluid which has just been poured into the stomach again flows out of it.

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[1] In cases of poisoning it may be absolutely necessary to use the stomach-pump, but in ordinary cases a tube should never be passed down the œsophagus until the absence of aortic aneurism has been ascertained by a careful examination of the patient's chest.

Intestine.—Drugs are applied to the intestine by means of enemata or suppositories. **Enemata** are liquid injections into the rectum for the purpose of emptying the lower parts of the bowels when we do not wish to excite the whole bowel, or when we wish to cause as little movement as possible to the patient. They are also used for the purpose of administering nutriment when the patient is unable to swallow or to retain food given by the mouth. In using enemata for the purpose of inducing action of the bowels the quantity should be considerable—sixteen fluid ounces, or even more. When they are intended to be retained, the quantity is usually small—not more than two to four fluid ounces at most. In using the enema syringe care should be taken that it is first emptied of air and that it is not pushed forcibly into the bowel. The nozzle should not be directed too much backward, as, if this be done, and especially if force be employed, ulceration of the posterior wall of the rectum may be induced. Where enemata are given for the purpose of nutrition, a much larger quantity than four ounces may be retained by using the proper method. A flexible, soft rubber tube should be passed for eight or ten inches up the intestine and the nutrient enema may then be slowly and gently introduced either by using a syringe or by simply pouring it into the tube by a funnel. By this method the fluid is introduced into the sigmoid flexure or descending colon, and if the patient can be propped somewhat so as to lie on his left side, none of it may descend into the rectum. In this case there will be little or no tendency to evacuate it and the whole may be readily absorbed.

The retention of a nutritive enema may be aided by folding a soft napkin so as to form a pad, and pressing it firmly against the anus for a few minutes after the enema has been given, and until the desire to evacuate the bowel has passed away.

Suppositories are drugs made up into a conical shape by means of cacao-butter. When introduced into the rectum the cacao-butter melts, the drugs become spread over the surface of the mucous membrane of the rectum and gradually absorbed. They are employed when we wish to get the local action of a drug upon the rectum, or the parts surrounding it, or when we wish to get the general action of a drug after its absorption without producing any local effect upon the stomach.

Application of Drugs to the Urethra.—They are usually employed as lotions. The syringe used to inject them should

FIG. 163.—Vulcanite syringe for injecting solutions into the urethra.

not have a small thin nozzle, but should have a conical point, such as that shown in Fig. 163, which fills up the opening of the

urethra and allows the injection to be forced up to the neck of the bladder without any escaping.

Application of Drugs to the Vagina and Uterus.—Lotions are usually either injected into the vagina with a syringe, or allowed to flow into it from a reservoir at some height above the patient. In either case, if it is desirable that the lotion should remain in contact with the vaginal walls or cervix uteri, the patient should lie on her back with the hips raised by a pillow. The syringe employed for the vagina is usually furnished with a shield to prevent it from being introduced too far, and it ought to have no central opening, but only openings at the side, as occasionally, when astringent and irritating fluids have been used with syringes having a central aperture, they have been forced into the cavity of the uterus, and have there produced uterine contraction and consequent pain. Sedative and astringent substances are often introduced in the form of **pessaries** or vaginal suppositories, in which the active substance is mixed with either cacao-butter or with gelatine and glycerin. Solids such as **caustics** are applied either to the vaginal walls or cervix directly through a speculum, and powders are applied on pledgets of cotton-wool. **Tents,** consisting of thin sticks of a porous substance, are introduced into the cervix itself for the purpose of dilating it, and solutions may be injected into the uterine cavity itself by means of a syringe provided with a long nozzle.

CHAPTER XVIII.

ANTIDOTES.

Antidotes are remedies which **counteract** the effect of **poisons.**

Action.—Antidotes may act in two ways; they may either **prevent** the action of the poison on the body, or they may **counteract** its effects. Many of them, especially those which are employed in the case of mineral poisons, form chemical compounds with the poisons which are almost insoluble and therefore inert.

Some of these compounds though nearly insoluble will nevertheless be gradually dissolved and absorbed if left too long in the stomach, and therefore it is advisable to remove them by means of **emetics** or by the **stomach-pump** or stomach-syphon as soon as possible. Indeed, it is advisable **in all cases of poisoning,** when the substance has been taken into the stomach, to **empty the stomach** at once before proceeding to administer the antidote. The only possible **exception** is when a highly corrosive substance has been taken which may have partially dissolved the wall of the stomach and rendered it extremely liable to rupture during emesis, or on the introduction of a stomach-tube. If the poison has been absorbed, we must try to counteract its poisonous action on the respiration, circulation, or temperature, by giving substances which will tend to produce an opposite effect.

The more common poisons with their antidotes are given in the following table:—

Poisonous Gases.

Sulphuretted hydrogen.	Chlorine cautiously inhaled.
Chlorine . . . . . Bromide . . . . . Iodine vapour . . .	Steam inhalations.
Vapour of ammonia .	Vapour of vinegar.
Carbon monoxide . .	Fresh air and artificial respiration. Transfusion.

Poisonous Gases—*continued.*

Nitrous oxide . . .	Artificial respiration, with the tongue drawn forward, and with intermittent pressure over the cardiac region if the heart is failing.
Coal gas . . . . . Charcoal fumes . . . Carbonic acid (choke damp) . . . . . Marsh gas . . . . Fire damp	Artificial respiration. Alternate warm and cold douche to the head and chest. Friction. Mustard plasters over surface.

Acids.

Acids— Sulphuric . . . . Hydrochloric . . . Nitric . . . . . Phosphoric . . .	Alkalies— Bicarbonate of sodium or potassium. Magnesia. Chalk or whiting. Plaster from the wall. Soap. Milk. Eggs beaten up. Olive or almond oil.
Oxalic acid . . . . . Bin-oxalate of potassium (salts of lemon or salts of sorrel) . Tartaric acid . . . Acetic acid	Chalk or whiting, or plaster from the wall, with water.
Hydrocyanic acid . .	Alternate cold and warm affusions. Artificial respiration. Injection of atropine (2 to 4 minims of liquor atropinæ) repeated every half-hour. Per- and proto- salts of iron, with magnesia, are recommended to render the acid insoluble, but it acts so quickly that there is usually no time for their application.

Alkalies.

Caustic potash or soda Caustic lime . . . . Caustic ammonia . . Carbonate of sodium or potassium	Vinegar. Lemon juice. Other dilute acids. Milk. Oil.

	Alkaloids, &c.
Aconite	Spirits. Ammonia. Warmth. Digitalis. Atropine.
Alcohol	Coffee. Cold douche to head.
Anæsthetics Chloroform, ether, &c.	Artificial respiration, inversion, &c.
Antimony	If vomiting does not occur wash out the stomach with water first; then with tannic or gallic acid; then give milk and white of egg as demulcent to stomach.
Arsenic	Wash out the stomach with large draughts of warm water, either by the stomach-pump, or if the arsenic itself does not cause vomiting, by using sulphate of zinc. Give magnesia, or still better, freshly precipitated oxide of iron made by precipitating a solution of perchloride of iron with carbonate of sodium or with ammonia. Dialysed iron is also very useful.
Atropine	Give stimulants and coffee; inject caffeine subcutaneously; arouse from stupor, as in opium-poisoning, and, if necessary, artificial respiration. Give cautiously physostigma.
Barium salts	Give Epsom or Glauber's salts or dilute sulphuric acid.
Belladonna. *Vide* Atropine.	
Burnett's Disinfecting Fluid. *Vide* Metallic Salts.	
Calabar bean	Stimulants. Atropine. Artificial respiration if necessary.
Cannabis Indica. *Vide* Morphine.	
Cantharides	Large quantity of demulcent drinks. Barley water. Gruel. Linseed tea. Avoid oils and fats.

Alkaloids, &c.

Carbolic acid . . .	Saccharated lime. Stimulants.
Cherry laurel water.	*Vide* Hydrocyanic Acid.
Chloral	Keep patient warm. Arouse him. Give him coffee per rectum. Liquor strychninæ, 4 minims, subcutaneously, repeated every 10 to 20 minutes, if necessary.
Bichromate of potassium.	Same as Acids.
Colchicum	Tannic or Gallic acid. Stimulants.
Conium	Tannic acid. Stimulants. Coffee.
Quinine	Tannic or Gallic acid. Strong tea or coffee. Stimulants warmed. Artificial respiration.
Copper. *Vide* Metallic Salts.	
Corrosive sublimate. *Vide* Metallic Salts.	
Creasote. *Vide* Carbolic Acid.	
Croton oil	Demulcents. Stimulants.
Curare	Artificial respiration. If there is a wound, ligature above it if possible, and incise and suck strongly. The ligature should be loosened from time to time, and again tightened, so as not to let too much poison into the blood at once.
Cyanide of potassium.	*Vide* Hydrocyanic Acid.
Digitalis	Strong tea. Tannin. Stimulants. Aconite, 5 minims of the tincture subcutaneously. Keep perfectly quiet, lying in bed.
Ergot	Tannin. Stimulants.

Alkaloids, &c.

Gelsemium	Atropine. Stimulants. Artificial respiration.
Hyoscyamus. *Vide* Atropine.	
Insect powder. *Vide* Arsenic.	
Laburnum	Stimulants. Coffee. Alternate hot and cold douches to chest.
Lead. *Vide* Metallic Salts.	
Lobelia	Tannin. Stimulants. Strychnine hypodermically (5 minims of liq. strychninæ).
Metallic salts	White of egg freely to form insoluble compound: then wash out stomach to remove it: afterwards demulcents. Poultices to surface, and morphine if necessary.
Morphine	Warm coffee after the stomach is emptied. Ammonia. Arouse by flicking with a towel, or by galvanic battery, and keep awake by walking about and renewal of stimulation if necessary. 2 to 4 minims of liq. atropinæ subcutaneously. Artificial respiration, if necessary.
Mushrooms	2 to 4 minims liq. atropinæ, subcutaneously: repeat if necessary. Castor oil. Stimulants.
Nitro-benzol Nitrite of Amyl	Stimulants. Alternate hot and cold douche. Artificial respiration.
Nitro-glycerin	Cold to head. Ergotin. Atropine, subcutaneously.
Oil of Bitter Almonds. *Vide* Hydrocyanic acid.	
Opium. *Vide* Morphine.	
Phosphorus	Sulphate of copper. Oil of turpentine, old and oxidised. Avoid oils and fats.

Alkaloids, &c.

Physostigma . . .	Stimulants. Atropine. Chloral. Strychnine. Artificial respiration.
Picrotoxine	Chloral. Bromide of potassium.
Pilocarpine	Atropine.
Rat-paste. *Vide* Phosphorus.	
Savin	Epsom salts. Demulcents.
Snake-bite	Ligature limb, cut out part with pen-knife and sear with hot iron. Alcoholic stimulants. Ammonia. Artificial respiration.
Stramonium. *Vide* Atropine.	
Strychnine	Chloroform. Tannin. Bromide of potassium. Chloral.
Tobacco	Tannin. Stimulants, warm. Strychnine.
Turpentine (oil of) . .	Demulcents. Sulphate of magnesium.
Veratrine.	Stimulants. Coffee, warm. Recumbent posture.
Vermin-killer. *Vide* Strychnine.	

CHAPTER XIX.

ANTAGONISTIC ACTION OF DRUGS.

The idea that one drug might be made to counteract the deadly effects of another is a very old one, and in the middle ages alexipharmics and mithridates were used as antidotes. Of late years, however, the subject has been investigated experimentally, and a more accurate knowledge of it obtained. Amongst the first of these experimental researches were those of Preyer, on the antagonism of atropine and hydrocyanic acid; of Schmiedeberg and Koppe on the antagonism of muscarine and atropine; and of Fraser on the antagonism between physostigma and atropine.

Although the fact is undisputed that we are occasionally able by the administration of one drug, to prevent the appearance of certain symptoms which would otherwise have certainly been produced by another previously administered, it is by no means certain that the one simply counteracts the effect of the other.

Some regard the effect of one drug in counteracting another as a case of chemical combination or substitution, the second drug either becoming added on to a compound of the first with some of the tissues, or else displacing it from such a compound with the tissues. Others, again, think that no chemical action of this sort takes place, but that each drug acts upon the tissue or tissues by itself—one, for example, exciting, and the other paralysing.

In favour of the first view may be mentioned the analogy between the action of poisons and the formation of acid-albumin and alkali-albumin, either of which can be changed into the other by excess of alkali or of acid respectively.

The objection is a very natural one that the doses of alkaloids required to produce marked physiological action are so extremely small that one can hardly fancy any chemical action being the cause of their physiological action. I have, however, on one occasion, by the addition of a single drop of liquor potassæ, converted a milky-looking fluid, consisting of the nuclei of fowl's blood-corpuscles suspended in water and measuring 90 cc., into a solid jelly-like mass—a result more striking than if a similar quantity injected into a frog had induced rigor in every muscle. Even such a result is infinitely less delicate than the colour reactions by which alkaloids are detected.

Some of the best-marked examples of antagonism in regard to involuntary muscular fibre are those observed by Ringer in the frog's heart, and they strongly support the view which he advocates of chemical substitution. As already mentioned, calcium salts and veratrine greatly prolong the cardiac systole; but this prolongation is at once removed, and the systole rendered normal by a small quantity of a potassium salt. The salts of potassium alone render the systole short and weaker, and then normal, but this action again is neutralised by calcium.

A similar condition has been observed by Cash and myself in the voluntary muscles of the frog. The contraction of the gastrocnemius is prolonged to a slight extent by calcium, and to a great extent by veratrine, and also by barium salts. This contraction is quickly reduced to the normal by the addition of a small quantity of potash.

There is no very well-marked case of antagonism, in which one drug is able to restore power to motor nerves which have been paralysed by another drug; such antagonism, however, has been observed in regard to the vagus. By small doses of atropine this may be paralysed; by a dose of physostigma administered afterwards the inhibitory power may again be restored; and by a further dose of atropine it may be again paralysed. This action has been denied by Rossbach, but in experiments on the subject by myself, I have obtained this effect in such a marked degree that I have no doubt regarding it. It is possible that the different results obtained may be due partly to the animal employed, partly to the dose, partly to the preparations of the drug, and partly to the temperature at which the experiments are made.[1] In my experiments the vagus was irritated, and I ascertained that the stimulation was strong enough to stop the heart. A very small quantity of atropine was then injected, and the same stimulus was repeated. After enough atropine had been gradually injected to abolish the inhibitory action of the vagus completely, some physostigma was injected into the jugular vein, and the irritation again repeated with the effect of stopping the heart as at first.

The antagonism of certain drugs upon the frog's heart has received much attention. In considering this subject care must be taken to distinguish between experiments made with the ventricle alone, containing involuntary muscular fibres but no ganglia, and the whole heart, in which both muscle and ganglia are contained. The experiments on veratrine, calcium, and potassium, already alluded to, were made with the ventricle alone; those which are now to be considered have reference to

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[1] My experiments were made on rabbits during the summer. The preparation of physostigma employed was a glycerin extract of the bean, and the preparation of atropine used was the Liquor Atropinæ, B.P. (1875).

the whole heart. Atropine appears to have the power not only of destroying the inhibitory action of the vagus upon the heart, but of antagonising those drugs which inhibit the heart and render its beats slower, or stop them altogether, such as muscarine, physostigma, pilocarpine, and phytolacca. Digitalin and saponin have a mutually antagonistic power, so that when the frog's heart has been stopped by either of them, the other will restore its pulsations. A limited antagonism also exists between muscarine, aconitine, and digitalin; when the heart has been stopped by digitalis, muscarine and aconite will restore its movements. Digitalin will also restore the pulsations in a heart which has been arrested by aconite. Physostigmine, camphor, and other drugs which stimulate the muscular fibre of the heart will remove the still-stand caused by muscarine.

Another very important antagonism is that between drugs acting on the respiratory centre and spinal cord. The mode of action of these drugs is difficult to explain on account of our imperfect knowledge of the physiology of the structures on which they act. Chloral lessens the excitability of these structures, strychnine increases it. These drugs have to a certain extent an antagonistic action, so that a fatal dose of strychnine may be so antagonised by chloral as to prevent death; and a small quantity of strychnine may prevent death from chloral. Atropine has an exciting action on the respiratory centre, somewhat like strychnine though very much less marked; and atropine also will antagonise chloral. It has also an antagonistic action to aconite, which has a peculiar depressing influence on the respiratory centre.

The sedative action of chloral enables it to antagonise picrotoxine which has a stimulant action on the brain causing convulsions. Opium and belladonna have to a certain extent an antagonistic action to one another. The first point which appeared to indicate an antagonistic action was their different effect on the pupil; but probably the point on which they chiefly antagonise one another is their action on respiration, atropine acting as a stimulant and morphine as a depressant to the respiratory centre.

The alkaloids of tea, coffee, and allied substances, viz. theine or caffeine, cocaine and guaranine, are antagonistic to morphine. These alkaloids in small and moderate doses increase the irritability of the brain, spinal cord, heart, and vaso-motor system, and in large doses paralyse them. Morphine and these alkaloids to a certain extent counteract one another, so that a lethal dose of one may be prevented from causing death by administering the other.

The antagonism of drugs is also marked in regard to their action on the glandular system; thus the excessive salivation produced by physostigma, pilocarpine, and bromal may be

arrested by atropine, which also arrests the excessive secretion from the skin caused by pilocarpine, and the secretion from the mucous membrane of the lungs produced by bromal.

The following table shows the most important examples of antagonism. The lethal and antagonistic doses have only been ascertained for a few. When the remark 'not antagonistic' occurs in the table, it means that the second drug mentioned will not prevent death from a lethal dose of the first, although the first will prevent death from a lethal dose of the second.

TABLE SHOWING THE ANTAGONISM OF DRUGS.

		Lethal dose.—I.	Lethal dose.—II.	Antidotal doses
Aconitine	Atropine	$\frac{1}{900}$th	7	$\frac{1}{750}$th
"	Digitalin	$\frac{1}{900}$th	1	$\frac{1}{600}$th
"	Strychnine	$\frac{1}{900}$th	$\frac{1}{288}$th	$\frac{1}{750}$th
Alcohol	Strychnine	—	$\frac{1}{288}$th	
Ammonium chloride	Chloral	—		
Atropine	Aconitine	7	$\frac{1}{900}$th	not antagonistic
"	Bromal-hydrate	7	$1\frac{1}{4}$	not antagonistic
"	Chloral-hydrate	7	7	
"	Hydrocyanic acid	7		
"	Jaborandi	7		
"	Muscarine	7		
"	Morphine	7	3	not antagonistic
"	Physostigmine	7	$\frac{1}{25}$th	
"	Phytolacca	7		
"	Pilocarpine	7		
"	Quinine	7		
Barium	Sodium sulphate			
"	Potassium salts			
Bromal-hydrate	Atropine	$1\frac{1}{4}$	7	
Brucine	Chloral			
Calabarine	"			
Carbolic acid	"			
Chloral	Ammonium chloride			
"	Atropine			
"	Brucine			
"	Calabarine			
"	Carbolic acid			
"	Codeine			
"	Physostigma			
"	Picrotoxine			
"	Strychnine			
"	Thebaine			
Chloroform	Amyl nitrite			
Cocaine	Morphine			
Codeine	Chloral			
Digitalin	Aconitine			
"	Muscarine			
"	Saponin			
Gelsemium	Opium			
"	Atropine			

TABLE SHOWING THE ANTAGONISM OF DRUGS—*continued.*

		Lethal dose.—I.	Lethal dose.—II.	Antidotal doses
Morphine . .	Atropine			
,, . .	Caffeine			
,, . .	Chloroform . . .			
,, . .	Cocaine			
,, . .	Daturine . . .			
,, . .	Hyoscyamine . . .			
,, . .	Nicotine . . .			
,, . .	Physostigma . . .			
Muscarine .	Atropine			
Opium . .	,, ...			
,, . .	Gelsemium . . .			
,, . .	Veratrum viride . .			
Physostigma .	Atropine			
,, . .	Chloral			
,, . .	Morphine . . .			
Saponin . .	Digitalin			
Strychnine .	Alcohol			
,, . .	Chloral			
,, . .	Hydrocyanic acid . .			
,, . .	Nicotine			
,, . .	Nitrite of amyl . .			
Thebaine . .	Chloral			

CHAPTER XX.

DOSAGE.

The circumstances which affect dosage have already been discussed (p. 37). In practice we reckon the dose according to age, making allowances, however, for the size and sex of the patient. Various tables have been drawn up for this purpose. One in common use is Dr. Young's. It is to convert the age into a fraction by adding twelve to it and using the number thus obtained as the denominator, the age itself being the enumerator. Thus, if a child's age be three years, the denominator will be $3 + 12 = 15$, and the enumerator will be 3. The dose for the child will therefore be $\frac{3}{3+12} = \frac{3}{15} = \frac{1}{5}$ of that for an adult. For a child five years old it will be $\frac{5}{5+12} = \frac{5}{17}$, which is between one-third and one-fourth of that for an adult. If the child is large for its years, we would give one-third; if small, we would rather give one-fourth.

Another rule, proposed by Dr. Cowling, is to divide the number of the patient's *next* birthday by twenty-four. Thus, for a child three years old, the fraction representing the dose would be $\frac{4}{24} = \frac{1}{6}$; for a child five years old, $\frac{6}{24} = \frac{1}{4}$.

The rule which I should propose as being more convenient for the metric system is a modification of Dr. Cowling's. If we assume that the body has attained its full growth at twenty-five years of age instead of twenty-four, we get the proportion by dividing the number of the next birthday by twenty-five. Thus, for a child three years of age, the proportion would be $\frac{4}{25} =$ nearly $\frac{1}{6}$; for a child five years of age, $\frac{6}{25} =$ between $\frac{1}{5}$ and $\frac{1}{4}$. This number does not lend itself readily to fractions such as the preceding, but it is very easy to divide by twenty-five by simply multiplying by four and dividing by 100. When the metrical system is used, all that is necessary is to multiply the full dose by the number of the child's next birthday, then by four, and remove the decimal point two places to the left. Thus, if the full dose for an adult be 1 gramme, the dose for a child of three will be $\frac{1 \times 4 \times 4}{100} = \cdot 160$ gramme or 16 centigrammes. If the full dose for an adult be ·3 gramme, the dose for a child of three will be $\frac{\cdot 3 \times 4 \times 4}{100} = \cdot 048$, or 48 milligrammes. If the full dose be 1 gramme,

the dose for a child of five will be $\frac{1 \times 6 \times 4}{100} = \cdot 240$ gramme or 24 centigrammes. If the full dose be ·3 gramme, the dose for a child of five will be $\frac{\cdot 3 \times 6 \times 4}{100} = \cdot 072$ gramme or 72 milligrammes.

To put this rule shortly, the number of grammes in the full dose multiplied by the child's next birthday and by four, gives the result in centigrammes. The number of decigrammes multiplied in the same way gives the result in milligrammes.

SECTION II.

GENERAL PHARMACY.

CHAPTER XXI

PHARMACEUTICAL PREPARATIONS.

Pharmacy includes both the general preparation of drugs from crude natural products and their combinations with other substances, so as to render them either more effectual or more easily administered.

The great rule for the administration of medicines is (1) **curare** (2) **cito**, (3) **tute, et** (4) **jucunde**— that they shall not only (1) cure, but that they shall do so (2) quickly, (3) safely, and (4) pleasantly. According to this rule many prescriptions contain four ingredients, viz.: (1) the substance which is to cure, or the *basis*; (2) the *adjuvant* to help it; (3) the *corrective* to prevent any bad effects; and (4) the *vehicle* to make it pleasant to take. This rule, however, is carried out not only in written prescriptions, but in those also which have been adopted by the profession at large, as a means of saving labour and time in the routine of practice, and embodied in the Pharmacopœia as useful preparations.

Formerly we were dependent for our medicines chiefly on the crude products of the animal, vegetable, and mineral kingdoms. As chemistry advanced various inorganic compounds were discovered and added to the Materia Medica, and as our knowledge of this science becomes greater and our power of preparing various organic bodies increases, we find that such bodies are becoming more and more introduced into medicine. As examples of these, we may take carbolic acid, chloral, chloroform, ether, hydrocyanic acid, iodoform, nitrite of amyl, salicylic acid, and kairin.

We seem now on the verge of discovering the mode of preparation of many organic alkaloids, and when this has been done, the vegetable Materia Medica will be less important than it is now, inasmuch as it is probable that, by using artificial alkaloids, prepared always under similar conditions, we may obtain purer products and greater constancy of action than we can at present from the natural active principles.

Recent discoveries have shown that plants generally contain active principles so closely associated, that the mixture was regarded as a pure alkaloid, and yet these drugs have very different

and sometimes opposite physiological actions. Thus ordinary coniïne usually contains pure coniïne and methyl-coniïne, the former of which paralyses the motor nerves, while the latter paralyses the spinal cord. Extract of physostigma, and supposed pure physostigmine, or eserine, have been found to contain two active principles, viz. physostigmine having a paralysing action, and calabarine having a tetanising action on the spinal cord.

The power which chemistry now gives us also of modifying the chemical constitution of organic bodies and therewith their physiological action, will almost certainly enable us to treat disease much more perfectly than we can at present. For such modified drugs, however, we must be indebted to the chemist. He will prefer to operate on substances which have been already prepared by himself rather than on crude drugs obtained from plants. But at present we are still dependent on the vegetable kingdom for a large number of our most useful remedies. In plants they are associated, as a rule, with quantities of woody tissue which is quite inert and indigestible, and which would interfere very much both with their easy administration and with their action.

Sometimes the crude drug is given in the form of a simple **powder**, without any admixture, as in the case of guaiac given in tonsillitis, where it is advisable to have the local action of the drug on the throat, as well as its general action on the system. Sometimes the powder may be readily given by enveloping it in a **wafer**, and swallowing it with a little water, and at other times it is made up with saccharine, and more or less adhesive substances, into the form of a **confection** or **bolus**; or suspended in water by means of mucilage in the form of a **mixture**. Usually however the active parts of the drug are extracted by means of solvents, and either given in solution, or in the solid form, after the solvents have been evaporated. There are a number of preparations according to the solvents used, and the mode in which they are applied. Probably the most convenient arrangement is not to take the groups of preparations according to the solvents or mode of preparation, but alphabetically for the sake of reference.

Groups of Officinal Preparations.

The letters B.P. stand for the British Pharmacopœia of 1885, and U.S.P. for the United States Pharmacopœia of 1883. When the letters B.P. or U.S.P. *precede* the name of a class or of a substance, they indicate that it is contained in the corresponding pharmacopœia only, and not in the other. They succeed the name or are omitted when the class or substance occurs in both pharmacopœias. When there are differences between things bearing the same name in the British and United States Pharmacopœias, the letters B.P. are placed after the descriptions of

that contained in the British, and U.S.P. after that of the United States Pharmacopœia.

U.S.P. Abstracta. ABSTRACTS.—These are very dry, powdered extracts. They are twice the strength of the crude drug, and about twice the strength of the corresponding fluid extracts. They are prepared by extracting the active principles from 200 parts of the crude drug by percolation with the strong or diluted alcohol, mixing the percolate with some sugar of milk, letting it dry, and then adding sufficient sugar of milk to make up the product to 100 parts. They are eleven in number.

	DOSE.		DOSE.
Abstractum Aconiti	$\frac{1}{4}$–1 gr.	Abstractum Ignatiæ	$\frac{1}{2}$–$1\frac{1}{2}$ gr.
„ Belladonnæ	$\frac{1}{2}$–1 gr.	„ Jalapæ	5–15 gr.
„ Conii	1–3 gr.	„ Nucis Vomicæ	$\frac{1}{2}$–2 gr.
„ Digitalis	$\frac{1}{2}$–1 gr.	„ Podophylli	5–10 gr.
„ Hyoscyami	2–3 gr.	„ Senegæ	1–3 gr.
		„ Valerianæ	10–20 gr.

Aceta. VINEGARS.—These are solutions of medicines in vinegar or acetic acid. In the B.P. there are three, in the U.S.P. there are four.

B.P.	DOSE.	U.S.P.	DOSE.
Acetum.		Acetum Lobeliæ	30–60 min.
„ Cantharidis		„ Opii	10–15 min.
„ Scillæ	15–60 min.	„ Sanguinariæ	3–4 fluid dr.
		„ Scillæ	15–60 min.

Alkaloidea. ALKALOIDS.—These are organic bases which may be regarded as compound ammonias.

Like ammonia they all contain nitrogen, and form salts with acids. Most of them contain oxygen in addition to nitrogen, carbon, and hydrogen, and occur as crystalline solids. Some, e.g. coniïne, nicotine, sparteine, piperidin, contain no oxygen, and occur as oily liquids. They generally have a powerful physiological action. They occur in many exogenous plants, but only veratrine and substances nearly allied to it have been obtained from the class of endogens and muscarine from thallogens. They occur in the plants in combination with acids. The alkaloids themselves are generally soluble in alcohol, but sparingly soluble in water. Their salts are more soluble in water. The general plan of obtaining them is to prepare an aqueous solution either of the salt originally present in the plant, or of one formed by treatment with an acid, and to precipitate them by an alkali, generally ammonia, from it. As the alkaloids are soluble in alcohol they would be very imperfectly precipitated, or not at all, if the ammonia were added to an alcoholic solution of their salts.

In the B.P. of 1867 the names of alkaloids all terminated in 'ia,' like ammonia, e.g. quinia, strychnia. Chemists have now generally returned to the older nomenclature, and assign the termination 'ine' to alkaloids, e.g. strychnine, quinine. To neutral principles they give the termination 'in,' e.g. santonin

salicin. This terminology has been followed in the B.P. of 1885 and the U.S.P. of 1883.

General Properties and Reactions of Alkaloids. – Alkaloids are basic in nature, like ammonia, forming salts with acid radicals, easily decomposed by the action of alkalies and alkaline carbonates.

Alkaloids are, for the most part, insoluble in water, with the exception of brucine and codeine, which are readily soluble; they are all soluble in alcohol, benzene, and chloroform. Their salts are soluble in water, and have the property of turning the plane of polarised light to the left: cinchonine, conchinine, coniïne, laudanosine, however, turn the plane to the right. Some alkaloids have no effect on polarised light, e.g. berberine, cryptopine, emetine, hydrocotarnine, narceïne, veratrine, caffeine, and piperine.

In solution, alkaloids are precipitated by a solution of iodine in iodide of potassium, by potassio-mercuric iodide, and a similar double iodide of cadmium and bismuth, also by picric acid and by phospho-molybdic and phospho-tungstic acids.

B.P.

Aconitina (Aconitine).
Apomorphinæ Hydrochloras (Hydrochlorate of Apomorphine).
Atropina (Atropine).
Atropinæ Sulphas.
Beberinæ Sulphas (Sulphate of Beberine).
Caffeina (Caffeine).
Caffeinæ Citras (Citrate of Caffeine).
Cinchonidinæ Sulphas (Sulphate of Cinchonidine).
Cinchoninæ Sulphas (Sulphate of Cinchonine).
Cocainæ Hydrochloras (Hydrochlorate of Cocaine).
Codeina (Codeine).
Morphinæ Acetas (Acetate of Morphine).
,, Bimeconatis Liquor (Solution of Bimeconate of Morphine).
,, Hydrochloras (Hydrochlorate of Morphine).
,, Sulphas (Sulphate of Morphine).
Physostigmina (Physostigmine).
Pilocarpinæ Nitras (Nitrate of Pilocarpine).
Quininæ Hydrochloras (Hydrochlorate of Quinine).
Quininæ Sulphas (Sulphate of Quinine).
Strychnina (Strychnine).
Strychninæ Hydrochloras (Hydrochlorate of Strychnine).
Veratrina (Veratrine).

U.S.P.

Apomorphina (Apomorphine).
Atropina (Atropine).
Atropinæ Sulphas (Sulphate of Atropine).
Caffeina (Caffeine).
Cinchonidinæ Sulphas (Sulphate of Cinchonidine).
Cinchonina (Cinchonine).
Cinchoninæ Sulphas (Sulphate of Cinchonine).
Codeina (Codeine).
Hyoscyaminæ Sulphas (Sulphas of Hyoscyamine).
Morphina (Morphine).
Morphinæ Acetas (Acetate of Morphine).
Morphinæ Hydrochloras (Hydrochlorate of Morphine).
,, Sulphas (Sulphate of Morphine).
Physostigminæ Salicylas (Salicylate of Physostigmine).
Pilocarpinæ Hydrochloras (Hydrochlorate of Pilocarpine).
Piperina (Piperine).
Quinidinæ Sulphas (Sulphate of Quinidine).
Quinina (Quinine).
Quininæ Bisulphas (Bisulphate of Quinine).
Quininæ Hydrobromas (Hydrobromate of Quinine).
,, Hydrochloras (Hydrochlorate of Quinine).
,, Sulphas (Sulphate of Quinine).

U.S.P.

Quininæ Valerianas (Valerianate of Quinine).
Strychnina (Strychnine).
Strychninæ Sulphas (Sulphate of Strychnine).
Veratrina (Veratrine).

Chinoidinum (Chinoidin or Quinoidin), U.S.P., is a mixture of bases.

Along with the alkaloids may be mentioned several **neutral principles** which resemble alkaloids in having a powerful physiological action.

B.P.	U.S.P.
Aloin.	*Chrysarobinum* (*Chrysarobin*).
Chrysarobinum (*Chrysarobin*).	Picrotoxinum (Picrotoxin).
Elaterinum (Elaterin).	Salicinum (Salicin).
Ergotinum (*Ergotin*).	Santoninum (Santonin).
Salicinum (Salicin).	
Santoninum (Santonin).	

The substances whose names are printed in italics in the above list are not pure principles. The chrysarobinum of the pharmacopœias is a mixture of substances containing chrysarobin and chrysophanic acid, and ergotin is only a purified extract of ergot. Lupulinum (B.P.) is only a glandular powder derived from hops, although from the sound of its name it might be supposed to be an active principle.

Aquæ. WATERS. (16 in B.P.; 15 U.S.P.)—One is simply water, another distilled water. The others in the B.P. are water containing small quantities of volatile oils in solution, with the exception of two, aqua chloroformi and aqua laurocerasi, which contain chloroform and hydrocyanic acid respectively instead of a volatile oil. Two waters are prepared by simply dissolving the substances in them in the cold; these are aqua camphoræ and aqua chloroformi. All the rest are prepared by distillation. Two are prepared by distilling the volatile oils with water; these are peppermint and spearmint waters. All the rest are prepared by distilling the plant in a retort with water and continuing the process until a certain quantity is distilled over.

In the U.S.P. aqua ammoniæ, aqua ammoniæ fortior, and aqua chlori consist of solutions of ammoniacal and chlorine gases in water. One, the aqua creasoti, consists of a solution of one part of creasote in 100 of water.

The others consist of volatile oils in water. Only two, aqua aurantii florum and aqua rosæ, are prepared by distilling the flowers with water. The others are prepared by thoroughly distributing the requisite quantity of volatile oil through a quantity of cotton, and dissolving it in water, by allowing the latter to percolate through. Camphor is dissolved in alcohol before adding it to the cotton.

Waters are chiefly **used** as vehicles.

The dose of all those in the B.P. with one exception is from half an ounce to two ounces. This exception is aqua laurocerasi, which is not used as a vehicle, but is, on the contrary, a powerful drug containing hydrocyanic acid, and the dose of it is very small, 5–30 minims.

Aqua anethi is a favourite remedy for flatulence in children, and in them it is given in a dose of a teaspoonful or more.

B.P. (16).	DOSE.
Aqua	
,, Destillata.	
,, Anethi	$\frac{1}{2}$–2 oz.
,, Anisi	,,
,, Aurantii Floris	,,
,, Camphoræ	,,
,, Carui	,,
,, Chloroformi	,,
,, Cinnamomi	,,
,, Fœniculi	,,
,, Laurocerasi	5-30 minims.
,, Menthæ Piperitæ	$\frac{1}{2}$–2 oz.
,, Menthæ Viridis	,,
,, Pimentæ	,,
,, Rosæ	,,
,, Sambuci	,,

U.S.P. (15).	DOSE.
Aqua	
,, Destillata.	
,, Ammoniæ	10-30 minims
,, Ammoniæ Fortior.	
,, Amygdalæ Amaræ	2 drachms.
,, Anisi	$\frac{1}{2}$–2 oz.
,, Aurantii Florum	,,
,, Camphoræ	,,
,, Chlori	,,
,, Cinnamomii	$\frac{1}{2}$–2 fluid oz.
,, Creasoti	1–4 drachms.
,, Fœniculi	1–2 fluid oz.
,, Menthæ Piperitæ	,,
,, Menthæ Viridis	,,
,, Rosæ	,,

B.P. Cataplasmata. CATAPLASMS OR POULTICES. (6.)—These are used as a means of applying externally moisture and warmth, and in certain cases medicaments, to parts of the body. They consist of linseed meal or of bread crumb, made into a paste with hot water. In one, cataplasma conii, hemlock leaf is added to relieve pain; in another, cataplasma sinapis, mustard is used to stimulate the skin; and in the cataplasma carbonis, cataplasma fermenti, and cataplasma sodæ chlorinatæ, wood charcoal, yeast, and chlorinated soda respectively, are added for the purpose of removing fœtor or acting as disinfectants.

B.P. (6).

Cataplasma Carbonis.
,, Conii.
,, Fermenti.
Cataplasma Lini.
,, Sinapis.
,, Sodæ Chlorinatæ.

U.S.P. Cerata. CERATES.—These are ointments containing wax. The admixture of wax with oil or lard in cerates renders them harder than ointments, though they are softer than plasters. They can be spread on linen or leather, at ordinary temperatures, without requiring heat like plasters, and they can be applied to the skin without melting and running like ointments.

U.S.P. (8).

Ceratum.
,, Camphoræ.
,, Cantharidis.
,, Cetacei.
Ceratum Extracti Cantharidis.
,, Plumbi Subacetatis.
,, Resinæ.
,, Sabinæ.

Chartæ. PAPERS.—Charta epispastica or cantharidis, and charta sinapis, consist of irritating substances spread upon paper,

and used for the purpose of producing rubefaction or vesication. Charta potassii nitratis consists of bibulous paper soaked in a solution of nitrate of potassium and dried, and is used for burning to give relief in asthma by inhalation of the fumes.

B.P. (2).	U.S.P. (3).
Charta Epispastica.	Charta Cantharidis.
„ Sinapis.	„ Potassii Nitratis.
	„ Sinapis.

Collodia. COLLODIONS.—In these collodion is used as a solvent and means of application.

B.P. (3).	U.S.P. (3).
Collodium.	Collodium.
„ Flexile.	„ cum Cantharide.
„ Vesicans.	„ Flexile.
	„ Stypticum.

Confectiones. CONFECTIONS, ELECTUARIES OR CONSERVES.—These are soft pastes which contain the drug mixed with sugar or honey, and are convenient forms of administering drugs, which would be unpleasant to take alone, and would be too bulky for pills. In two of them, the confection of dog roses, and of red roses, the drug is of itself inert, and the confection is used only as a vehicle; in the others, the drug is active, and the confection is used as a mode of administering it. The dose of all is 1 to 2 drachms, with the exception of the confection of opium (B.P.) and of scammony (B.P.).

B.P. (8).	DOSE.	U.S.P. (2).	DOSE.
Confectio Opii	5–20 grs.	Confectio Rosæ.....................	
„ Piperis...............		„ Sennæ	1–2 dr.
„ Rosæ Caninæ......			
„ Rosæ Gallicæ......			
„ Scammonii.........	10–30 grs.		
„ Sennæ...............			
„ Sulphuris			
„ Terebinthinæ			

Decocta. DECOCTIONS.—These are made by boiling the drug with water, and then straining while hot. Usually the boiling is continued from ten to twenty minutes, in order to dissolve out the active part of the drug; prolonged boiling frequently alters it, and may render it inert.

B.P. (13).	DOSE.	U.S.P. (2).	DOSE.
Decoctum Aloes Compositum	½–1 fl. oz.	Decoctum Cetrariæ..............	ad lib.
„ Cetrariæ	ad lib.	„ Sarsaparillæ Compositum............	4–6 fl. oz.
„ Cinchonæ [Rubræ]	1–2 fl. oz.		
„ Granati Radicis ...	„		
„ Hæmatoxyli.........	„		
„ Hordei	ad lib.		
„ Papaveris	for external use.		
„ Pareiræ...............	1–2 fl. oz		
„ Quercus	„		

B.P.	DOSE.
Decoctum Sarsæ	2–10 fl. oz.
„ Sarsæ Compositum	„
„ Scoparii	2–4 fl. oz.
„ Taraxaci	„

U.S.P. Elixiria. Elixirs. — These are diluted tinctures rendered agreeable by aromatics and sugar. The only one in the U.S.P. is used as a vehicle.

U.S.P. (1).
Elixir Aurantii (Simple Elixir).

Emplastra. Plasters.—These consist of adhesive substances spread upon leather or cloth, so as to stick to the part of the body to which they are applied.

Lead plaster is one of the most important, as it forms a basis for other plasters. It is also used for covering slight wounds and excoriations. Resin plaster is more adhesive, and is used to hold the edges of wounds together and to apply pressure. Two others, emplastrum belladonnæ and emplastrum opii, contain narcotic substances with the intention of lessening pain locally. The others are used for the purpose of affording mechanical support or gentle stimulation, and emplastrum cantharidis (B.P.) is used as a vesicant.

B.P. (14).

Emplastrum Ammoniaci cum Hydrargyro.
„ Belladonnæ.
„ Calefaciens (warming).
„ Cantharidis.
„ Ferri.
„ Galbani.
„ Hydrargyri.
„ Opii.
„ Picis.
„ Plumbi.
„ „ Iodidi.
„ Resinæ.
„ Saponis.
„ „ Fuscum.

U.S.P. (17).

Emplastrum Ammoniaci (Ammoniac).
„ „ c. Hydrargyro (ammoniac with mercury).
„ Arnicæ (Arnica).
„ Asafœtidæ (Asafœtida).
„ Belladonnæ (Belladonna).
„ Capsici (Capsicum).
„ Ferri (Iron).
„ Galbani (Galbanum).
„ Hydrargyri (Mercurial).
„ Icthyocollæ (Court).
„ Opii (Opium).
„ Picis Burgundicæ (Burgundy pitch).
„ Picis Canadensis (Hemlock pitch).
„ Picis cum Cantharide (warming).
„ Plumbi (Diachylon).
„ Resinæ (adhesive).
„ Saponis (Soap).

B.P. Enemata. Injections, Enemas, or Clysters.—These are preparations for injection into the rectum. When the quantity injected is large, and especially if cold, it is usually returned almost immediately; therefore, when we wish to get it retained, a small quantity only, and warm, must be employed. The vehicle in most injections is starch mucilage. In the enema of aloes 10 ounces, and in those of Epsom salts and of turpentine, 15 ounces of the vehicle are used, and these enemata are em-

ployed for the purpose of evacuating the bowel. In the case of the enema opii which we wish to be retained the quantity is only 2 ounces. This is used both as a local and general sedative, in order to relieve pain in or about the pelvis, or to produce the general action of opium after its absorption, in cases where medicines cannot be retained by the stomach, or when it is unadvisable to administer them by the mouth. The enema asafœtidæ is perhaps the most powerful remedy we possess in cases of tympanitic distension of the bowels. As it is used for the purpose of exciting the contraction of the bowels and the expulsion of flatulence, but not of simply evacuating the rectum, an intermediate quantity is used, viz. 4 ounces. Asafœtida contains a gum as well as a resin, and therefore no mucilage is required to suspend it, and water only is required in preparing it.

The enema of tobacco is now so rarely used, on account of the danger from collapse, that it has been omitted from the B.P. of 1885; but formerly, before the introduction of chloroform, it was frequently employed in order to cause muscular relaxation of voluntary and involuntary muscles in hernia, tetanus, obstruction of the bowels, &c.

B.P. (5). NONE IN U.S.P.

Enema Aloes (aloes 40 grains, potassium carbonate 15 grains).
„ Asafœtidæ (asafœtida 30 gr., water 4 fl. oz.).
„ Magnesii Sulphatis (sulphate of magnesium 1 oz., olive oil 1 fl. oz.).
„ Opii (tincture of opium ½ fl. dr.).
„ Terebinthinæ (oil of turpentine 1 fl. oz.).

B.P. Essentiæ. Essences.—These are strong solutions of 1 part volatile oil in 4 of rectified spirit. They are used as carminatives, and are usually given in the form of a few drops on a piece of lump sugar, or with a little hot sugar and water, in order to remove flatulence.

B.P. (2).	DOSE.
Essentia Anisi	10-20 m.
„ Menthæ Piperitæ	10–20 m.

Extracta. Extracts.—Extracts consist of the soluble parts of plants reduced to the consistence of a thick paste by extraction and evaporation. The plan of treatment adopted in order to extract the soluble parts, and leave behind the woody fibre and other inert constituents varies, according as the plant is fresh or dry.

From fresh plants, green extracts (B.P.) are obtained by evaporation of the fresh juice after removal of the coagulable albumin. From dried plants the active principles are removed by treatment with cold or boiling water, with spirit, ether, or acetic acid, and the solutions thus obtained are evaporated to a consistence suitable for making pills, or else to dryness.

Where the active principles are of a resinous or alkaloidal nature, and are more soluble in pure than in dilute spirit,

alcohol or rectified spirit is used; in other cases dilute alcohol or proof spirit is employed. Where the drug contains more than one active substance and one is more soluble in spirit, and the other in water, both spirit and water are used. In order to prevent extracts which, when freshly prepared, are of a proper consistence for making pills, from becoming too dry and hard by keeping, the U.S.P. in several instances directs them to be mixed with 5 per cent. of glycerine.

B.P. (34).	DOSE.
Extractum Aconiti	1–2 gr.
,, Aloes Barbadensis	2–6 gr.
,, ,, Socotrinæ	,,
,, Anthemidis	2–10 gr.
,, Belladonnæ	$\frac{1}{4}$–1 gr.
,, ,, Alcoholicum	$\frac{1}{16}$–$\frac{1}{4}$ gr.
,, Calumbæ	2–10 gr.
,, Cannabis Indicæ	$\frac{1}{4}$–1 gr.
,, Cascaræ Sagradæ	2–8 gr.
,, Colchici	$\frac{1}{2}$–2 gr.
,, ,, Aceticum	$\frac{1}{2}$–2 gr.
,, Colcynthidis Compositum	3–10 gr.
,, Conii	2–6 gr.
,, Gelsemii Alcoholicum	$\frac{1}{2}$–2 gr.
,, Gentianæ	2–10 gr.
,, Glycyrrhizæ	10–30 gr.
,, Hæmatoxyli	,,
,, Hyoscyami	5–10 gr.
,, Jaborandi	2–10 gr.
,, Jalapæ	5–15 gr.
,, Krameriæ	5–20 gr.
,, Lactucæ	5–15 gr.
,, Lupuli	,,
,, Mezerei Æthereum	
,, Nucis Vomicæ	$\frac{1}{2}$–2 gr.
,, Opii	$\frac{1}{2}$–2 gr.
,, Papaveris	2–5 gr.
,, Pareiræ	10–30 gr.
,, Physostigmatis	$\frac{1}{16}$–$\frac{1}{4}$ gr.
,, Quassiæ	3–5 gr.
,, Rhamni Frangulæ	15–20 gr.
,, Rhei	5–15 gr.
,, Stramonii	$\frac{1}{4}$–$\frac{1}{2}$ gr.
,, Taraxaci	5–30 gr.

U.S.P. (31).	DOSE.
Extractum Aconiti	$\frac{1}{6}$–$\frac{1}{4}$ gr
,, Aloes Aquosum	2–10 gr.
,, Arnicæ Radicis	3–5 gr.
,, Belladonnæ Alcoholicum	$\frac{1}{4}$ gr.
,, Cannabis Indicæ	,,
,, Cinchonæ	10–30 gr.
,, Colchici Radicis	1–2 gr.
,, Colocynthidis	$\frac{1}{2}$–1 gr.
,, ,, Compositum	5–30 gr.
,, Conii Alcoholicum	$\frac{1}{2}$–1 gr.
,, Digitalis	$\frac{1}{4}$ gr.
,, Ergotæ	5–15 gr.
,, Euonymi	1–3 gr.
,, Gentianæ	10–30 gr.
,, Glycyrrhizæ	ad lib.
,, ,, Purum	ad lib.
,, Hæmatoxyli	10–30 gr.
,, Hyoscyami Alcoholicum	1–2 gr.
,, Iridis	1–2 gr.
,, Juglandis	5–10 gr.
,, Krameriæ	10–20 gr.
,, Leptandræ	20–30 gr.
,, Malti	1–4 dr.
,, Mezerei	
,, Nucis Vomicæ	$\frac{1}{2}$–2 gr.
,, Opii	$\frac{1}{2}$–1 gr.
,, Podophylli	1–3 gr.
,, Physostigmatis	$\frac{1}{12}$–$\frac{1}{6}$ gr.
,, Quassiæ	1–2 gr.
,, Rhei	5–10 gr.
,, Stramonii	$\frac{1}{4}$–$\frac{1}{2}$ gr.
,, Taraxaci	20–60 gr.

Fluid U.S.P. or Liquid B.P. Extracts.—These are made like watery extracts, excepting that instead of evaporating the infusion, decoction, or alcoholic solution (U.S.P.) to a solid paste, it is only reduced to a small bulk, and in the B.P. some spirit is added to it in order to prevent decomposition.

B.P. (13).	DOSE.
Extractum Belæ Liquidum	1–2 fluid drachms.
,, Cascaræ Sagradæ Liquidum	$\frac{1}{2}$–2 fluid drachms.
,, Cimicifugæ Liquidum	3–30 minims.
,, Cinchonæ ,,	10–30 minims.
,, Cocæ ,,	$\frac{1}{2}$–2 fluid drachms.
,, Ergotæ ,,	10–30 minims.

B.P.	DOSE.
Extractum Filicis Liquidum	15–60 minims.
" Glycyrrhizæ "	60–120 minims.
" Opii "	10–40 minims.
" Pareiræ "	½-2 fluid drachms.
" Rhamni Frangulæ Liquidum	1–4 fluid drachms.
" Sarsæ Liquidum	2–4 fluid drachms.
" Taraxaci Liquidum	¼–2 fluid drachms.

U.S.P. (79).	DOSE.
Extractum Aconiti Fluidum	½–1 m. (0·03–0·06 c.c.).
" Arnicæ Radicis Fluidum	5–10 m. (0·3–0·6 c.c.).
" Aromaticum "	10–20 m. (0·6–1·25 c.c.).
" Aurantii Amari "	15–30 m. (0·9–1·9 c.c.).
" Belladonnæ "	1–2 m. (0·06–0·12 c.c.).
" Brayeræ "	½–1 fl. oz. (15–30 c.c.).
" Buchu "	30–60 m. (1·9–3·8 c.c.).
" Calami "	5–15 m. (0·3–0·9 c.c.).
" Calumbæ "	15–30 m. (0·9–1·9 c.c.).
" Cannabis Indicæ "	½–1 m. (0·03–0·06 c.c.).
" Capsici "	½–1 m. (0·03–0·06 c.c.).
" Castaneæ "	1–2 fl. dr. (3·75–7·5 c.c.)
" Chimaphilæ "	1 fl. dr. (3·75 c.c.).
" Chiratæ "	½ fl. dr. (1·9 c.c.).
" Cimicifugæ "	½–1 fl. dr. (1·9–3·75 c.c.).
" Cinchonæ "	¼–2 fl. oz. (7·5–60 c.c.).
" Colchici Radicis "	2–8 m. (0·12–0·5 c.c.).
" " Seminis "	2–8 m. (0·12–0·5 c.c.).
" Conii "	5 m. (0·3 c.c.).
" Cornus "	30 m. (1·9 c.c.).
" Cubebæ "	10-40 m. (0·6-2·5 c.c.).
" Cypripedii "	15 m. (0·9 c.c.).
" Digitalis "	1–2 m. (0·06–0·12 c.c.).
" Dulcamaræ "	30–60 m. (1·9–3·75 c.c.).
" Ergotæ "	½–4 fl. dr. (1·9–15 c.c.).
" Erythroxyli "	20–60 m. (1·25–3·75 c.c.).
" Eucalypti "	5-10 m. (0·3–0·6 c.c.).
" Eupatorii "	20–60 m. (1·25–3·75 c.c.).
" Frangulæ "	10–20 m. (0·6–1·25 c.c.).
" Gelsemii "	2–3 m. (0·12–0·18 c.c.).
" Gentianæ "	10–30 m. (0·6–1·9 c.c.).
" Geranii "	30–60 m. (1·9–3·75 c.c.).
" Glycyrrhizæ "	30–120 m. (1·9–7·5 c.c.).
" Gossypii Radicis "	30–60 m. (1·9–3·75 c.c.).
" Grindeliæ "	30–60 m. (1·9–3·75 c.c.).
" Guaranæ "	1–2 fl. dr. (3·75–7·5 c.c.).
" Hamamelidis "	30 m. (1·9 c.c.).
" Hydrastis "	1–2 fl. dr. (3·75–7·5 c.c.).
" Hyoscyami "	5 m. (0·3 c.c.).
" Ipecacuanhæ "	15–30 m. (0·9–1·9 c.c.).
" Iridis "	5–10 m. (0·3–0·6 c.c.).
" Krameriæ "	10–60 m. (0·6–3·75 c.c.).
" Lactucarii "	5–30 m. (0·3–1·9 c.c.).
" Leptandræ "	20–60 m. (1·25–3·75 c.c.).
" Lobeliæ "	10-20 m. (0·6–1·25 c.c.).
" Lupulini "	10–15 m. (0·6–0·9 c.c.).
" Maticæ "	30–60 m. (1·9–3·75 c.c.).
" Mezerei "	for external use.
" Nucis Vomicæ "	3-5 m. (0·18–0·3 c.c.).
" Pareiræ "	1–2 fl. dr. (3·75–7·5 c.c.).
" Pilocarpi "	15–30 m. (0·9–1·9 c.c.).
" Podophylli "	5–15 m. (0·3–0·9 c.c.)
" Pruni Virginianæ "	30–60 m. (1·9–3·75 c.c.).

U.S.P.	DOSE.
Extractum Quassiæ Fluidum	5–10 m. (0·3–0·6 c.c.).
„ Rhei „	5–30 m. (0·3–1·9 c.c.).
„ Rhois Glabræ „	for external use.
„ Rosæ „	1–2 fl. dr. (3·75–7·5 c.c.).
„ Rubi „	½–1 fl. dr. (1·9–3·75 c.c.).
„ Rumicis „	1 fl. dr. (3·75 c.c.).
„ Sabinæ „	3–8 m. (0·18–0·5 c.c.).
„ Sanguinariæ „	3–5 m. (0·18–0·3 c.c.).
„ Sarsaparillæ „	2–4 fl. dr. (7·5–15 c.c.).
„ Sarsaparillæ Compositum „	30–60 m. (1·9–3·75 c.c.).
„ Scillæ „	1–3 m. (0·12–0·18 c.c.).
„ Scutellariæ „	30–60 m. (1·9–3·75 c.c.).
„ Senegæ „	1–5 m. (0·06–0·3 c.c.).
„ Sennæ „	1–4 fl. dr. (3·75–15 c.c.).
„ Serpentariæ „	20–30 m. (1·25–1·9 c.c.).
„ Spigeliæ „	1–2 fl. dr. (3·75–7·5 c.c.).
„ Stillingiæ „	15–45 m. (0·9–2·8 c.c.).
„ Stramonii „	1–2 m. (0·06–0·12 c.c.)
„ Taraxaci „	1–3 fl. dr. (3·75–11·25 c.c.).
„ Tritici „	3–6 fl. dr. (11·25–22·5 c.c.).
„ Uvæ Ursi „	30–60 m. (1·9–3·75 c.c.).
„ Valerianæ „	1 fl. dr. (3·75 c.c.).
„ Veratri Viridis „	1–2 m. (0·06–0·12 c.c.).
„ Viburni „	30–60 m. (1·9–3·75 c.c.).
„ Xanthoxyli „	30–60 m. (1·9–3·75 c.c.).
„ Zingiberis „	10–20 m. (0·6–1·25 c.c.).

B.P. Fresh or Green Extracts.—These extracts have already been enumerated among the others. In preparing them, the juice obtained from the fresh leaves, flowering tops or fruits, of the plant, by pressure, is heated to 130° F. to coagulate the green colouring matter. This is then filtered off and laid aside. The filtrate is next heated to 200° F. so as to coagulate the albumin; this is filtered off and thrown away. The filtrate is then evaporated at a temperature not exceeding 140° to a thin syrup. The colouring matter is then added to it, and the whole evaporated to a proper consistence. In the case of extracts of colchicum and taraxacum there is no chlorophyll to separate, as the juices are obtained by expression from the colchicum corm and the taraxacum root, and not from flowering tops. Consequently the juice is at once heated to the boiling point to coagulate the albumin, and after this has been filtered out the filtrate is evaporated at a temperature of 160° F. In the case of green extracts, the preservation of the green colour is usually regarded as a sign that they are good. It certainly indicates that the first and the last parts of the process have been conducted with care, as too high a temperature destroys the green colour. It is therefore probable that the whole process may have been carefully done; but this is not certain, for the juice may have been exposed to a high temperature, and thus injured during its evaporation after the chlorophyll has been removed and before it has again been added.

The green extracts of the B.P. are (8):—

Extractum Aconiti.	Extractum Colchici Aceticum.	Extractum Lactucæ.
,, Belladonnæ.	,, Conii.	,, Taraxaci.
,, Colchici.	,, Hyoscyami.	

Glycerina, B.P.; Glycerita, U.S.P. GLYCERINES.—These are solutions of soothing, astringent, or antiseptic substances in glycerine. Glycerine being thick and adhesive, they form most useful local applications, either to the skin or mucous membranes.

Those in the B.P. containing carbolic, tannic, and gallic acids have one part of the drug by weight to four of glycerine by measure; starch, being very light and bulky, is used in only half this proportion, i.e. one ounce of starch to eight ounces of glycerine. In the U.S.P. the starch is in the proportion of 1 to 9, i.e. 10 per cent. The glyceritum vitelli contains 45 parts fresh yolk of egg to 55 of glycerine.

B.P. (9).	U.S.P. (3).
Glycerinum.	Glycerinum.
,, Acidi Carbolici (1 to 4).	Glyceritum Amyli (1 in 10).
,, ,, Gallici (1 to 4).	,, Vitelli ($4\frac{1}{2}$ in 10).
,, ,, Tannici (1 to 4).	
,, Aluminis (1 to 5).	
,, Amyli (1 to 8).	
,, Boracis (1 to 6).	
,, Plumbi Subacetatis.	
,, Tragacanthæ (3 to 14).	

Infusa. INFUSIONS.—These are prepared by simply pouring boiling water on the drug, allowing it to stand for some time, and then straining.

There are four exceptions to this rule of using boiling water, viz. calumba, quassia, chiretta, and cusparia. Infusions of calumba and quassia are prepared with cold water. The reason for using cold water in the case of calumba is that the root contains a quantity of starch, which is extracted if hot water be used, and renders the infusion liable to decompose, especially in hot weather.

I have been unable to find any definite reason assigned for using cold water in the preparation of infusion of quassia, excepting that cold water is sufficient to dissolve the active principle.

In the only instance in which I have seen an infusion made with hot water used, it caused vomiting, so that perhaps an infusion made with hot water has a more irritating action than that made with cold.

Infusions of chiretta and cusparia are made with water at 120° F. instead of boiling water, as they are more agreeable when prepared in this way.

The infusions of substances not specified in the U.S.P. are directed by it to be prepared by taking ten parts of the substance

in coarse powder and 100 of boiling water. These are to be put into a vessel with a tight cover, and allowed to stand for two hours. The infusion is then strained, and enough water passed through the strainer to make the product weigh 100 parts.

All the infusions both of the B.P. and U.S.P. are strained, with the exception of the infusion of cusso or brayera.

B.P. (28).	DOSE. (Of all not specified 1–2 fl. oz.)	U.S.P. (5).	DOSE.
Infusum Anthemidis	1–4 fl. oz.	Infusum Brayeræ (Cusso)	10 oz.
,, Aurantii		,, Cinchonæ	2 oz.
,, ,, Compositum		,, Digitalis [1]	½ oz.
,, Buchu	1–4 fl. oz.	,, Pruni Virginianæ	2–3 oz.
,, Calumbæ		,, Sennæ Compositum	4 fl. oz.
,, Caryophylli			
,, Cascarillæ			
,, Catechu			
,, Chiratæ			
,, Cinchonæ Acidum			
,, Cuspariæ			
,, Cusso (Brayera anthelmintica)	4–8 fl. oz.		
,, Digitalis	1–4 fl. dr.		
,, Ergotæ			
,, Gentianæ Compositum			
,, Jaborandi			
,, Krameriæ			
,, Lini			
,, Lupuli			
,, Maticæ			
,, Quassiæ			
,, Rhei			
,, Rosæ Acidum			
,, Senegæ			
,, Sennæ			
,, Serpentariæ			
,, Uvæ Ursi			
,, Valerianæ			

B.P. Injectiones Hypodermicæ. HYPODERMIC INJECTIONS.—These are strong solutions for subcutaneous injection (p. 475). As the solutions may become decomposed by keeping, they should be freshly prepared; and even the injection of morphine should not be kept long. Any solid particles should be removed by filtration (p. 476). The injections of apomorphine and of ergotin are simply made by dissolving these substances in camphor water and filtering if necessary. The injection of morphine is prepared by dissolving freshly-precipitated morphine in acetic acid and water. It is ten times as strong as the liquor and is rather stronger than the corresponding preparation in the B.P. of 1867, containing 1 grain in 10 minims, instead of 1 grain in 12 minims.

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[1] This infusion is about twice the strength of the B.P. The dose is usually stated at ½ oz. twice a day, but in many cases this dose would probably prove too large, and it is safer to begin with a smaller dose, and gradually push it as the patient will stand it.

B.P.			DOSE.
Injectio Apomorphinæ Hypodermica		(2 in 100)	2–8 min.
,, Ergotini	,,	(1 to 2)	3–10 min.
,, Morphinæ	,,	(1 in 10)	1–5 min.

B.P. Lamellæ. GELATINE DISCS.—These are thin discs of gelatine with some glycerine, each weighing about $\frac{1}{50}$th grain and containing a small quantity of an alkaloid. They are chiefly used for local application to the eye. They may sometimes be convenient for preparing solutions for hypodermic injection by dissolving them in a few drops of water.

Lamellæ Atropinæ ($\frac{1}{5000}$th grain in each).
,, Cocainæ ($\frac{1}{200}$th grain in each).
,, Physostigminæ ($\frac{1}{1000}$th grain in each).

Linimenta. LINIMENTS OR EMBROCATIONS.—These are preparations for rubbing or painting on a part of the body in order to produce local stimulation or relieve pain. The basis of most of those in the British Pharmacopœia is olive oil, and of those in the United States Pharmacopœia cotton-seed oil.[1] Camphor is added to most of the liniments in the B.P. for its local stimulant action, and also that its strong smell may lessen the risk of the liniment being used internally. There are four exceptions in the B.P.—the liniments of ammonia, lime, croton oil, and iodide of potassium with soap. With the exception of the liniment of lime all these contain very strong smelling substances, namely, ammonia in the corresponding liniment, cajuput oil in the croton oil liniment, and oil of lemon in the iodide of potassium and soap liniment.

Camphor is not contained in the liniments of the U.S.P., with the exception of the liniments of belladonna, camphor, chloroform and soap.

Soap is used to give a lubricating quality to four liniments in the B.P., viz. opium, iodide of potassium with soap, soap and turpentine; and to two in the U.S.P., viz. chloroform and soap. In the compound mustard liniment, whose composition is nearly the same in the B.P. and the U.S.P., castor oil is used as a lubricant along with alcohol. In one, the turpentine liniment of the U.S.P., the lubricating substances are lard and yellow wax.

Three liniments in the B.P., aconite, belladonna, and iodine, and one in the U.S.P., belladonna, are really exceedingly strong solutions of active principles in spirit with camphor added for the purposes already mentioned.

The liniments last mentioned contain no fatty substances as lubricants, nor does the croton oil liniment of the B.P., compound camphor liniment (B.P.), nor the linimentum cantharidis (U.S.P.). Croton oil liniment (B.P.) is a solution of croton oil

[1] I have been told that a great deal of what is sold as olive oil in Great Britain is really cotton-seed oil.

with cajuput oil in spirit. The compound camphor liniment is a mixture of strong solution of ammonia with rectified spirit, camphor, and oil of lavender.

The linimentum cantharidis (U.S.P.) is a solution of the active principles of cantharides in turpentine. The difference in composition between the ordinary camphor liniment (B.P.), which is simply a mixture of camphor and olive oil, and the compound camphor liniment should be carefully borne in mind. The linimentum terebinthinæ aceticum (B.P.) consists of oil of turpentine and acetic acid mixed with ordinary camphor liniment. But if anyone, thinking to increase its efficacy, should add to it compound camphor liniment, the acetic acid and ammonia would neutralise one another more or less completely, and the activity of both liniments would be to a great extent destroyed.

B.P. (16).

The proportion of ingredients is put after each constituent.

Linimentum	**Basis**	**Solvent**	**Adjuvant**	**Vehicle**
Aconiti	Aconite root (20)	Rectified spirit (30)	Camphor (1)	
Ammoniæ	Liquor Ammoniæ (1)			Olive oil (3)
Belladonnæ	Belladonna root (20)	Rectified spirit (30)	Camphor (1)	
Calcis	Liquor Calcis (1)			Olive oil (1)
Camphoræ	Camphor (1)			Olive oil (4)
Camphoræ Compositum	Camphor (1)	Rectified spirit (6)	Liquor ammoniæ fortior (2)	
Chloroformi	Chloroform (1)			Liniment of Camphor (1)
Crotonis	Croton oil (2)	Rectified spirit (7)	Cajuput oil (7)	
Hydrargyri	Mercury ointment (1)		Liquor ammoniæ (1)	Liniment of Camphor (1)
Iodi	Iodine (5)	Iodide of Potassium (2)		Glycerine (1) Rectified spirit (40)
Opii	Tincture of Opium (1)			Liniment of Soap (1)
Potassii Iodidi cum Sapone	Iodide of Potassium (12)	Glycerine (8)	Curd Soap (16) Oil of Lemon (1)	Water (80)
Saponis	Hard Soap (16)	Water (32) Rectified spirit (128)	Camphor (8) Oil of Rosemary (3)	
Sinapis Compositum	Oil of Mustard (1·4)	Castor oil (7)	Ethereal extract of Mezereon (1) Camphor (3)	Rectified spirit (44)
Terebinthinæ	Oil of turpentine (16)		Camphor (1) Soft Soap	Water (2)
Terebinthinæ Aceticum	Oil of turpentine (4)		Glacial Acetic Acid (1)	Liniment of Camphor (4)

U.S.P. (10).

Linimentum	Basis	Solvent	Adjuvant	Vehicle
Ammoniæ .	Liquor Ammoniæ (3)			Cotton-seed oil (7)
Belladonnæ .	Fluid Extract of Belladonna (95)		Camphor (5)	
Calcis . .	Lime water (1)			Cotton-seed oil (1)
Camphoræ .	Camphor (1) .			Cotton-seed oil (4)
Cantharidis .	Cantharides (15)	Oil of Turpentine (85)		
Chloroformi .	Chloroform (4)			Soap liniment (6)
Plumbi Subacetatis	Solution of Subacetate of Lead (4)			Cotton-seed oil (6)
Saponis .	Soap (10)	Water (20) .	Camphor (5) . Oil of Rosemary	Alcohol (70)
Sinapis Compositum	Volatile Oil of Mustard (3)	Castor oil (15)	Extract of Mezereon (2) Camphor (6)	Alcohol (74)
Terebinthinæ .	Oil of Turpentine (35)		Resin Cerate (65)	

Liquores. SOLUTIONS.—These are solutions of active substances in water, either alone or with the aid of other solvents.

B.P. (48).	DOSE.
Liquor Acidi Chromici	
,, Ammoniæ	10–30 m.
,, ,, Fortior	3–10 m.
,, Ammonii Acetatis	2–6 fl. dr.
,, ,, ,, Fortior	25–75 m.
,, ,, Citratis	2–6 fl. dr.
,, ,, ,, Fortior	½–1½ fl. dr.
,, Antimonii Chloridi	
,, Arsenicalis	2–8 m.*
,, Arsenici Hydrochlorici	2–8 m.*
,, Arsenii et Hydrargyri Iodidi	
,, Atropinæ Sulphatis	1–4 m.*
,, Bismuthi et Ammonii Citratis	½–1 fl. dr.
,, Calcii Chloridi	
,, Calcis	1–4 fl. oz.
,, Calcis Chlorinatæ	
,, ,, Saccharatus	15–60 m.
,, Chlori	10–20 m.
,, Epispasticus	
,, Ferri Acetatis	
,, ,, ,, Fortior	
,, ,, Dialysatus	
,, ,, Perchloridi	10–30 m.
,, ,, ,, Fortior	

U.S.P. (27)	DOSE.
Liquor Acidi Arseniosi	2–8 m.
,, Ammonii Acetatis	½–1½ oz.
,, Arsenici et Hydrargyri Iodidi	5–10 m.
,, Calcis	2–4 fl. oz.
,, Ferri Acetatis	2–10 m.
,, ,, Chloridi	,,
,, ,, Citratis	10 m.
,, ,, et Quininæ Citratis	10–20 m.
,, ,, Nitratis	5–20 m.
,, ,, Subsulphatis	3–6 m.
,, ,, Tersulphatis	
,, Gutta-perchæ	
,, Hydrargyri Nitratis	
,, Iodi Compositus	5 m.
,, Magnesii Citratis	6–12 fl. oz.
,, Pepsini	½–2 fl. oz.
,, Plumbi Subacetatis	
,, ,, Subacetatis Dilutus	
,, Potassii	10–60 m.
,, ,, Arsenitis	5 m.
,, ,, Citratis	½–2 fl. oz.
,, Sodæ	10–60 m.
,, ,, Chloratæ	30–60 m.
,, Sodii Arseniatis	3–8 m.

B.P.	DOSE.	U.S.P.	DOSE.
Liquor Ferri Pernitratis	10–30 m.	Liquor Sodii Silicatis	
„ „ Persulphatis ...		„ Zinci Chloridi	
„ Gutta Percha			
„ Hydrargyri Nitratis Acidus			
„ Hydrargyri Perchloridi	½–2 fl. dr.		
„ Iodi	**		
„ Lithiæ Effervescens...	5–10 fl. oz.		
„ Magnesii Carbonatis .	1–2 fl. oz.		
„ „ Citratis......	5–10 fl. oz.		
„ Morphinæ Acetatis ...	10–60 m.*		
„ „ Bimeconatis			
„ „ Hydrochloratis	„		
„ Plumbi Subacetatis...			
„ „ „ Dilutus			
„ Potassæ	„		
„ „ Effervescens..	5–10 fl. oz.		
„ Potassii Permanganatis	1–4 fl. dr.*		
„ Sodæ	10–60 m.		
„ „ Effervescens	5–10 fl. oz.		
„ „ Chloratæ..........	10–20 m.		
„ Sodii Arseniatis	5–10 m.*		
„ „ Ethylatis.........			
„ Strychninæ Hydrochloratis	5–10 m.*		
„ Zinci Chloridi			

The strength of the liquors marked with an * in the preceding list has been changed from 4 grains to 1 fluid oz., or 1 in 109 (B.P. 1867) to 4½ grains in 1 fluid oz., or 1 in 100 in the B.P. 1885. The strength of the one marked ** has been increased from 5 in 109 to 5 in 100.

B.P. Lotiones. LOTIONS.—Mixtures of active substances in water for external application.

Lotio Hydrargyri Flava (1 part Perchloride of Mercury to 243 of Lime-water).
„ „ Nigra („ Subchloride „ 146 „).

U.S.P. Massæ. MASSES.—These simply consist of substances mixed together to a consistence suitable for making pills.

Massa Copaibæ.
„ Ferri Carbonatis.
„ Hydrargyri.

Mellita. HONEYS.—In these preparations honey is used as a vehicle. Oxymel and oxymel scillæ of the B.P., which contain acetic acid, may be regarded as belonging to this class.

B.P. (4).	U.S.P. (2).
Mel Boracis.	Mel Despumatum.
„ Depuratum.	„ Rosæ.
Oxymel.	
„ Scillæ.	

Misturæ. MIXTURES.—These usually consist of insoluble substances simply mixed with water or suspended in it by the aid of gum or other viscid substances. In almond (B.P. and

U.S.P.), chalk (B.P. and U.S.P.), guaiac (B.P.), and compound glycyrrhiza (U.S.P.) mixtures, gum is added. In the ammoniacum (B.P. and U.S.P.), asafœtida (U.S.P.) and compound iron (B.P. and U.S.P.) mixtures, gum is contained in the ammoniacum, asafœtida, and myrrh used in their preparation respectively.

In scammony mixture (B.P.) the scammony resin is simply suspended in milk. In egg flip or brandy mixture (mistura spiritus vini gallici) (B.P.) and chloroform mixture (U.S.P.) yolk of egg forms the basis of the mixture.

The magnesia and asafœtida,[1] and rhubarb and soda mixtures of the U.S.P. contain insoluble substances mixed with water without the addition of any viscid substance; in the creasote mixture (B.P.) the syrup may be looked upon as viscid and tending to keep the ingredients mixed, but the aromatic iron and compound senna mixtures of the B.P. and the acetate of iron and ammonium (U.S.P.) mixture are simply solutions and not mixtures in the usual sense.

B.P. (10).	DOSE.	U.S.P. (11).	DOSE.
Mistura Ammoniaci	½–1 fl. oz.	Mistura Ammoniaci	½–1 fl. oz.
„ Amygdalæ	1–2 fl. oz.	„ Amygdalæ	1–2 fl. oz.
„ Creasoti	„	„ Asafœtidæ	½–1 fl. oz.
„ Cretæ	„	„ Chloroformi	„
„ Ferri Aromatica	„	„ Cretæ	1–2 fl. oz.
„ „ Composita	„	„ Ferri Composita	„
„ Guaiaci	„	„ „ et Ammonii Acetatis	½–1 fl. oz.
„ Scammonii	„	„ Glycyrrhizæ Composita	½ oz.
„ Sennæ Composita	„	„ Magnesiæ et Asafœtidæ	20 m.
„ Spiritus Vini Gallici	„	„ Potassii Citratis	½ fl. oz.
		„ Rhei et Sodæ	½–1 dr.

Mucilagines. MUCILAGES.—These are thick solutions, partial or complete, of gum or starch, which are convenient for suspending heavy powders in mixtures.

B.P. (3).	U.S.P. (5).
Mucilago Acaciæ.	Mucilago Acaciæ.
„ Amyli.	„ Cydonii.
„ Tragacanthæ.	„ Sassafras Medullæ.
	„ Tragacanthæ.
	„ Ulmi.

Olea. OILS.—These are divided into fixed and volatile. The fixed are obtained by simple expression; the volatile by distillation excepting in the case of oil of lemon, which being contained in distinct vittæ in the rind, may be expressed instead of being distilled.

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[1] In this mixture there is no gum, for although it is contained in crude asafœtida, it is not contained in the tincture of asafœtida used in this preparation.

Fixed Oils.

B.P. (9).	DOSE.
Oleum Amygdalæ	1–4 fl. dr.
„ Crotonis (croton oil)	$\frac{1}{2}$–1 min.
„ Lini	
„ Morrhuæ	1–8 fl. dr.
„ Myristicæ Expressum	
„ Olivæ	„
„ Phosphoratum	5–10 min.
„ Ricini	1–8 fl. dr.
„ Theobromatis	

U.S.P. (11).	DOSE.
Oleum Adipis	
„ Amygdalæ Expressum	1–8 fl. dr.
„ Gossypii Seminis	
„ Lini	
„ Morrhuæ	$\frac{1}{2}$–4 fl. oz.
„ Olivæ	
„ Phosphoratum	1–5 min.
„ Ricini	1–8 fl. dr.
„ Sesami	
„ Theobromæ	
„ Tiglii (croton oil)	$\frac{1}{4}$–1 min.

Volatile Oils.

B.P. (25).	DOSE OF EACH. 1–4 m. unless otherwise mentioned.
Oleum Anethi	
„ Anisi	
„ Anthemidis	
„ Cajuputi	
„ Carui	
„ Caryophylli	
„ Cinnamomi	
„ Copaibæ	5–20 min.
„ Coriandri	
„ Cubebæ	5–20 min.
„ Eucalypti	
„ Juniperi	1–10 min.
„ Lavandulæ	
„ Limonis	
„ Menthæ Piperitæ	
„ „ Viridis	
„ Myristicæ	
„ Pimentæ	
„ Pini Sylvestris	for use as vapour.
„ Rosmarini	
„ Rutæ	
„ Sabinæ	
„ Santali	10–30 min.
„ Sinapis	For external use only.
„ Terebinthinæ	10–20 m. as diuretic, 2–6 fl. dr. as anthelmintic.

U.S.P. (40).	DOSE.
Oleum Æthereum	
„ Amygdalæ Amaræ	$\frac{1}{4}$–1 min (0·016–0·06 c.c.).
„ Anisi	5–15 min. (0·3–0·9 c.c.).
„ Aurantii Corticis	
„ „ Florum	
„ Bergamii	
„ Cajuputi	5–20 min. (0·3–1·25 c.c.).
„ Cari	1–10 min. (0·06–0·6 c.c.).
„ Caryophylli	2–6 min. (0·12–0·36 c.c.).
„ Chenopodii	4–8 min. for a child (0·25–0·5 c.c.).
„ Cinnamomi	1–3 min. (0·06–0·18 c.c.).
„ Copaibæ	10–15 min. (0·6–0·9 c.c.).
„ Coriandri	
„ Cubebæ	10–12 min. at first (0·6 or 0·72 c.c.), gradually increased.

Volatile Oils—*continued.*

U.S.P.	DOSE.
Oleum Erigerontis	10 min. to ½ fluid drachm (0·6–1·9 c.c.).
„ Eucalypti	10–15 min. (0·6–0·9 c.c.).
„ Fœniculi	5–15 min. (0·3–0·9 c.c.).
„ Gaultheriæ	
„ Hedeomæ (pennyroyal)	2–10 min. (0·12–0·6 c.c.).
„ Juniperi	5–15 min. (0·3–0·9 c.c.).
„ Lavandulæ	1–5 min. (0·06–0·3 c.c.).
„ „ Florum	
„ Limonis	
„ Menthæ Piperitæ	2–6 min. (0·12–0·36 c.c.).
„ „ Viridis	2–6 min. (0·06–0·36 c.c.).
„ Myrciæ	
„ Myristicæ	2–3 min. (0·12–0·18 c.c.).
„ Picis Liquidæ	
„ Pimentæ	3–6 min. (0·18–0·36 c.c.).
„ Rosæ	
„ Rosmarini	3–6 min. (0·18–0·36 c.c.).
„ Rutæ	2–5 min. (0·12–0·3 c.c.).
„ Sabinæ	2–5 min. (0·12–0·3 c.c.).
„ Santali	20–30 min. (1·25–1·9 c.c.).
„ Sassafras	3–5 min. (0·18–0·3 c.c.).
„ Sinapis Volatile	
„ Succini	5–15 min. (0·3–0·9 c.c.).
„ Terebinthinæ	5–30 min. (0·3–1·9 c.c.).
„ Thymi	
„ Valerianæ	4–5 min. (0·24–0·3 c.c.).

Oleata. OLEATES.—Solutions of bases in oleic acid. They are more readily absorbed by the skin than ointments.

B.P.	U.S.P.
Oleatum Hydrargyri.	Oleatum Hydrargyri.
„ Zinci.	„ Veratrinæ.

Oleoresinæ. OLEORESINS.—These are, as the name implies, mixtures of volatile oil and resin. They are extracted by treating the crude substance with stronger ether, and removing the ether partly by distillation and partly by evaporation. Their advantage is that they remain in a liquid or semi-liquid state, and are stable, not requiring alcohol to prevent decomposition.

B.P.	DOSE.
Oleoresina Cubebæ	5–30 min.

U.S.P.	DOSE.
Oleoresina Aspidii	½–1 fl. dr. (1·9–3·75 c.c.).
„ Capsici	¼–1 min. (0·015–0·06 c.c.).
„ Cubebæ	5–30 min. (0·3–1·9 c.c.).
„ Lupulini	2–5 gr. (0·13–0·33 gm.).
„ Piperis	¼–1 min. (0·015–0·06 c.c.).
„ Zingiberis	$\frac{1}{10}$–1 min. (0·006–0·06 c.c.).

Oxymel.—*Vide* MELLITA.

Pilulæ. PILLS.—Pills are small round masses which can be conveniently swallowed. They are rarely made of a greater

B.P. (21).

DOSE: 5–10 grains, with the exception of those mentioned.

Pilula	**Curare.**—Basis	Proportion of Basis	**Cito.**—Adjuvant	Proportion of Adjuvant	**Tute.**—Corrective	**Jucunde.**—Vehicle.	Dose
Aloes Barbadensis	Barbadoes Aloes	1 in 2	Hard Soap	1 in 4	Oil of Carraway	Confection of Roses	
Aloes et Asafœtidæ	Socotrine Aloes	1 in 4	" "	1 in 4	Asafœtida	" "	
Aloes et Ferri	Barbadoes Aloes	1 in $5\frac{1}{4}$	Sulphate of Iron	1 in 7	Compound Powder of Cinnamon	" "	
Aloes et Myrrhæ	Socotrine Aloes	1 in $2\frac{1}{4}$	Myrrh	1 in $4\frac{1}{2}$	Saffron	" "	
Aloes Socotrinæ	" "	1 in 2	Hard Soap	1 in 4	Volatile Oil of Nutmeg	" "	
Asafœtidæ Composita (*syn.* Galbani Composita)	Asafœtida	1 in $3\frac{1}{2}$	Galbanum	1 in $3\frac{1}{2}$	Myrrh	Treacle	
Cambogiæ Composita	Gamboge	1 in 5	Barbadoes Aloes Hard Soap	1 in 5 1 in 5	Compound Powder of Cinnamon	Syrup	
Colocynthidis Composita	Colocynth pulp	1 in 5	Barbadoes Aloes Scammony Sulphate of Potassium	1 in $2\frac{1}{2}$ 1 in $2\frac{1}{2}$ 1 in 20	Oil of Cloves	Water	
Colocynthidis et Hyoscyami	Compound pill of Colocynth	2 in 3	—	—	Extract of Henbane		
Conii Composita	Extract of Hemlock	5 in 6	Ipecacuanha	1 in 6	—	Treacle	
Ferri Carbonatis	Saccharated Carbonate of Iron	4 in 5	—	—	—	Confection of Roses	5–20 grs.
Ferri Iodidi	Iron Wine Iodine	—	—	—	Refined Sugar	Liquorice Root and Water	3–8 grs.
Hydrargyri	Mercury	1 in 3	—	—	Confection of Roses	Liquorice Root	3–8 grs.
Hydrargyri Subchloridi Composita	Subchloride of Mercury	1 in 5	Sulphurated Antimony	1 in 5	Guaiacum Resin (1 in $2\frac{1}{2}$)	Castor Oil	
Ipecacuanhæ cum Scillâ	Compound Powder of Ipecacuanha	3 in 5	Squill	1 in 5	Ammoniacum (1 in 5)	Treacle	
Phosphori	Phosphorus	1 in 90	Balsam of Tolu	1 in $2\frac{1}{4}$	Yellow Wax	Curd Soap	2–4 grs.
Plumbi cum Opio	Acetate of Lead	3 in 4	Opium	1 in 8	—	Confection of Roses	3–5 grs.

Rhei Composita .	Rhubarb Root . .	1 in $3\frac{3}{5}$	Socotrine Aloes . Hard Soap . .	1 in 5 1 in $7\frac{1}{3}$	Myrrh Oil of Peppermint .	Glycerine and Treacle	
Saponis Composita (*syn.* Opii)	Opium	1 in 5	—	—	Hard Soap . .	Glycerine . .	3–5 grs.
Scammonii Composita .	Resin of Scammony .	1 in 6	Resin of Jalap . Curd Soap . .	1 in 6 1 in 6	Strong Tincture of Ginger	Rectified Spirit .	5–15 grs.
Scillæ Composita . .	Squill	1 in $6\frac{1}{4}$	Ammoniacum .	1 in $6\frac{1}{4}$	Ginger	Hard Soap Treacle	
			U.S.P. (15). *Vide* also Massæ.				
Aloes	Purified Aloes . .	1 in 2	Soap	1 in 2	—	—	1–5 pills
Aloes et Asafœtidæ .	" " . .	1 in 3	"	1 in 3	Asafœtida . .		2–5 pills
Aloes et Ferri . .	" " . .	1 in 3	Sulphate of Iron .	1 in 3	Aromatic Powder .	Confection of Rose	1–3 pills
Aloes et Mastiches .	" " . .	2 in 3	—	—	Mastic . . .	Red Rose . .	1 pill
Aloes et Myrrhæ . .	" " . .	1 in $1\frac{3}{4}$	Myrrh . . .	1 in $3\frac{1}{2}$	Aromatic Powder .	Syrup . . .	3–6 pills
Antimonii Compositæ (Plummer's Pills)	Sulphurated Antimony.	1 in 4	Mild Chloride of Mercury	1 in 4	Guaiac . . .	Mucilage of Tragacanth	1–2 pills
Asafœtidæ . . .	Asafœtida . . .	3 in 4	—	—	—	Soap . . .	1 pill
Catharticæ Compositæ .	Compound Extract of Colocynth	1 in 3 (nearly)	Abstract of Jalap . Mild Chloride of Mercury . . Gamboge . .	1 in $3\frac{1}{2}$ 1 in $3\frac{1}{2}$ 1 in 14	—	Water . . .	1–3 pills
Ferri Compositæ . .	Sulphate of Iron . .	1 in 4	Carbonate of Sodium	1 in 4	Myrrh . . . Glycyrrhiza, Extract of Glycyrrhiza	Syrup . . . Sugar Balsam of Tolu	2–6 pills
Ferri Iodidi . .	Reduced Iron, Iodine .	—	—	—	Acacia	Stronger Ether .	1 pill
Galbani Compositæ .	Galbanum . . .	1 in $2\frac{1}{3}$	Myrrh . . .	1 in $2\frac{1}{3}$	Asafœtida . .	Syrup . . .	2–4 pills
Opii	Opium	1 in $1\frac{1}{4}$	—	—	—	Soap . . .	1 pill
Phosphori . . .	Phosphorus . . .	1 in 100	Althæa . . .	1 in $2\frac{1}{2}$	Acacia . . . Glycerin Chloroform . .	Balsam of Tolu . Stronger Ether	1–2 pills
Rhei	Rhubarb . . .	1 in $1\frac{1}{3}$	—	—	—	Soap . . .	1–6 pills
Rhei Compositæ . .	"	1 in $2\frac{1}{3}$	Aloes . . .	1 in 3	Myrrh . . . Oil of Peppermint	—	2–4 pills

weight than five grains, as they then become too bulky to be swallowed easily. Those of the U.S.P. are four grains each. In their composition the old rule of **curare cito, tute, et jucunde,** has been pretty strictly followed, and most of them in addition to the basis contain an adjuvant, corrective, and vehicle (see Table, pp. 522, 523). To prevent them sticking together they are generally shaken with some dry powder, such as lycopodium, carbonate of magnesium, flour, starch, or liquorice powder. Sometimes they are gilt or silvered by shaking them while freshly prepared, and without the addition of any dusting powder, along with gold or silver leaf in a hollow spherical wooden box. Sometimes pills are coated with sugar. Recently a coating of firm gelatine has been used, and perhaps the best coating of all in certain cases is keratin (*q. v.*).

Pulveres. POWDERS.—The fineness of powders is ascertained by the size of the meshes of the sieve through which they pass, and is represented by numbers ranging from No. 20 to No. 60, these numbers indicating the numbers of parallel wires of ordinary thickness within a linear inch forming the meshes of the sieves used. The officinal powders contain two or more substances triturated and mixed together.

B.P. (15).	DOSE.
Pulvis Amygdalæ Compositus	60–120 grs.
" Antimonialis	3–10 grs.
" Catechu Compositus	20–40 grs.
" Cinnamomi Compositus	3–10 grs.
" Cretæ Aromaticus	10–60 grs.
" " " cum Opio	10–40 grs.
" Elaterini Compositus	½–5 grs.
" Glycyrrhizæ Compositus	30–60 grs.
" Ipecacuanhæ Compositus	5–15 grs.
" Jalapæ Compositus	20–60 grs.
" Kino Compositus	5–20 grs.
" Opii Compositus	2–5 grs.
" Rhei Compositus	20–60 grs.
" Scammonii Compositus	10–20 grs.
" Tragacanthæ Compositus	20–60 grs.

U.S.P. (9).	DOSE.
Pulvis Antimonialis	3–8 grs. (0·2–0·52 gm.).
" Aromaticus	10–30 grs. (0·65–1·95 gm.).
" Cretæ Compositus	10–30 grs. (0·65–1·95 gm.).
" Effervescens Compositus	One powder.
" Glycyrrhizæ Compositus	30–60 grs. (1·95–3·9 gm.).
" Ipecacuanhæ et Opii	5–15 grs. (0·33–1 gm.).
" Jalapæ Compositus	30–60 grs. (1·95–3·9 gm.).
" Morphinæ Compositus	10 grs. (0·65 gm.).
" Rhei Compositus	30–60 grs. (1·95–3·9 gm.).

Resinæ. RESINS.—These are brittle, amorphous solids, consisting of an acid or mixtures of acids formed by the oxidation of terpenes which are volatile hydrocarbons having the formula $C_{10}H_{16}$. Resins are insoluble in water, but soluble in spirit. They melt when heated, and solidify again on cooling. They

dissolve in alkalies, forming a kind of soap. They frequently occur in plants along with unoxidised volatile oils as oleo-resins. Resins may be obtained from oleo-resins, e.g. turpentine, by simple distillation, when the volatile oil distils over and the resin remains. They may be got by heating the part of the plant in which they are contained, e.g. guaiac resin. They may be prepared by dissolving them out of the plants by means of alcohol and removing the alcohol by distillation, or precipitating them by throwing the strong tincture into water. Resins are of an acid nature, and the addition of a little mineral acid to water causes them to be precipitated more readily.

B.P. (5).	U.S.P. (5).
Resina.	Resina Copaibæ.
,, Guaiaci.	,, Jalapæ.
,, Jalapæ.	,, Podophylli.
,, Podophylli.	,, Scammonii.
,, Scammoniæ.	Guaiaci Resina.

Spiritus. SPIRITS.—With the exception of rectified and proof spirit, these are alcoholic solutions of volatile oils or ethers. The dose is ½ to 1 fluid drachm, except where otherwise mentioned, and except in the case of brandy, rum, and whisky, the doses of which vary very much, according to the purpose for which they are used.

B.P. (18).	DOSE.
Spiritus Ætheris	30–90 min.
,, ,, Compositus	½–2 fluid drachms.
,, ,, Nitrosi	,,
,, Ammoniæ Aromaticus	
,, ,, Fœtidus	
,, Armoraciæ Compositus	1–2 fluid drachms.
,, Cajuputi	
,, Camphoræ	10–30 min.
,, Chloroformi	10–60 min.
,, Cinnamomi	
,, Juniperi	½–1½ fluid drachms.
,, Lavandulæ	
,, Menthæ Piperitæ	
,, Myristicæ	
,, Rectificatus	
,, Rosmarini	10–60 min.
,, Tenuior	
,, Vini Gallici	

U.S.P. (22).	DOSE.
Spiritus Ætheris	1–3 fluid drachms (3·75–11·25 c.c.).
,, ,, Compositus	½–2 fluid drachms (1·0–7·5 c.c.).
,, ,, Nitrosi	30–60 min. (1·9–3·75 c.c.).
,, Ammoniæ	10–30 min. (0·6–1·9 c.c.).
,, ,, Aromaticus	30–60 min. (1·9–3·75 c.c.).
,, Anisi	1–2 fluid drachms (3·75–7·5 c.c.).
,, Aurantii	1–2 fluid drachms (3·75–7·5 c.c.).
,, Camphoræ	5–60 min. (0·3–3·75 c.c.).
,, Chloroformi	10–60 min. (0·6–3·75 c.c.).
,, Cinnamomi	10–20 min. (0·6–1·25 c.c.).
,, Frumenti (Whisky)	

U.S.P.	DOSE.
Spiritus Gaultheriæ	10–20 min. (0·6–1·25 c.c.).
„ Juniperi	30–60 min. (1·9–3·75 c.c.).
„ „ Compositus	2–4 fluid drachms (7·5–15 c.c.).
„ Lavandulæ	30–60 min. (1·9–3·75 c.c.).
„ Limonis	
„ Menthæ Piperitæ	10–20 min. (0·6–1·25 c.c.).
„ „ Viridis	30–40 min. (1·9–2·5 c.c.).
„ Myrciæ (Bay Rum)	
„ Myristicæ	1 fluid drachm (3·75 c.c.).
„ Odoratus (Cologne Water)	
„ Vini Gallici	

Suppositoria. SUPPOSITORIES. — These are small conical masses for introducing drugs into the rectum (p. 484). They are used either to produce a local action on the rectum itself, or on the adjoining pelvic organs, such as the uterus or the bladder; or to introduce certain drugs into the body when we wish to avoid any local action on the stomach.

Thus the morphine suppositories may be used for their general action in inducing sleep, or for their local action in soothing pain or irritation in the rectum or pelvic organs, or to check diarrhœa. The compound lead suppository may be used in diarrhœa for its local action on the rectum, and likewise for its general action in checking bleeding from the lungs, etc. The same may be said of the mercurial suppository. The others are more intended for local action.

The basis of the suppositories is cacao-butter (oil of theobroma), excepting in those where, as their name indicates, curd soap is used along with glycerine of starch.

B.P. (8).

Suppositoria Acidi Carbolici cum Sapone.
„ „ Tannici.
„ „ „ cum Sapone.
„ Hydrargyri.
„ Iodoformi.
„ Morphinæ.
„ „ cum Sapone.
„ Plumbi Composita.

In the U.S.P. no special suppositories are named, but a formula is given for their preparation. The quantity of the medicine required, brought to a proper consistency if necessary, is to be mixed with a small quantity of oil of theobroma by rubbing together, and then sufficient oil of theobroma previously melted and cooled to the temperature of 35° C. (95° F.) is to be mixed thoroughly with it, and immediately poured into suitable moulds cooled by ice. In the absence of moulds the mass is to be divided into parts of a definite weight, which are to be made into a convenient form for a suppository. Unless otherwise specified, they should weigh fifteen grains or one gramme.

Succi. JUICES.—These consist of the fresh juices of the plant, which are mixed with a sufficient quantity of spirit to

prevent them from decomposing, except in the case of lemon, mulberry, and buckthorn juice, to which no alcohol is added.

B.P. (7).

Succus Belladonnæ.
„ Conii.
„ Hyoscyami.
„ Scoparii.
Succus Taraxaci.
„ Limonis.
„ Mori.

U.S.P.
Succus Limonis.

Syrupi. Syrups.—These are strong solutions of sugar; many of them contain flavouring or colouring matters, and are used to make medicines more agreeable to the eye or palate.

In the case of the syrups containing ferrous salts the sugar prevents oxidation, and thus preserves the preparation from decomposition.

B.P. (17).	DOSE. All 1 fluid drachm except those specially marked.
Syrupus.	
„ Aurantii	
„ „ Floris	
„ Chloral	½–2 fluid drachms.
„ Ferri Iodidi	½–1 fluid drachm.
„ „ Phosphatis	
„ Hemidesmi	
„ Limonis	
„ Mori	
„ Papaveris	
„ Rhei	1–4 fluid drachms.
„ Rhœados	
„ Rosæ Gallicæ	
„ Scillæ	½–1 fluid drachm.
„ Sennæ	1–4 fluid drachms.
„ Tolutanus	
„ Zingiberis	½–1 fluid drachm.

U.S.P. (33).	DOSE.
Syrupus Acaciæ	
„ Acidi Citrici	
„ „ Hydriodici	1–4 fl. dr. (3·75–15 c.c.).
„ Allii	1 fl. dr. (3·75 c.c.).
„ Altheæ	1–4 fl. dr. (3·75–15 c.c.).
„ Amygdalæ	
„ Aurantii	
„ „ Florum	1 fl. dr. (3·75 c.c.).
„ Calcii Lactophosphatis	2–4 fl. dr. (7·5–15 c.c.).
„ Calcis	1 fl. dr. (3·75 c.c.).
„ Ferri Bromidi	½–1 fl. dr. (1·9–3·15 c.c.).
„ „ Iodidi	15–30 m. (0·9–1·9 c.c.).
„ „ Quininæ et Strychninæ Phosphatum	1 fl. dr. (3·75 c.c.).
„ Hypophosphatum	1–2 fl. dr. (3·75–7·5 c.c.).
„ „ cum Ferro	1–2 fl. dr. (3·75–7·5 c.c.).
„ Ipecacuanhæ	(Emetic) ½–1 oz. (15–30 c.c.). (Expectorant) 30–60 m. (1·9–3·75 c.c.)
„ Krameriæ	½ fl. oz. (15 c.c.).
„ Lactucarii	2–3 fl. dr. (7·5–11·25 c.c.).
„ Limonis	
„ Picis Liquidæ	1–2 fl. dr. (3·75–7·5 c.c.).
„ Pruni Virginianæ	½ fl. oz. (15 c.c.).

U.S.P.	DOSE.
Syrupus Rhei	1 fl. dr. (3·75 c.c.).
,, ,, Aromaticus	1 fl. dr. (3·75 c.c.).
,, Rosæ	1 fl. dr. (3·75 c.c.).
,, Rubi	1–2 fl. dr. (3·75–7·5 c.c.).
,, ,, Idæi	
,, Sarsaparillæ Compositus	½ fl. oz. (15 c.c.).
,, Scillæ	1 fl. dr. (3·75 c.c.).
,, ,, Compositus	(Expectorant) 20–30m. (1 25–1·9 c.c.).
,, Senegæ	1–2 fl. dr. (3·75–7·5 c.c.).
,, Sennæ	1–4 fl. dr. (3·75–15 c.c.).
,, Tolutanus	
,, Zingiberis	1 fl. dr. (3·75 c.c.).

B.P. Tabellæ. Tablets of chocolate each weighing 2½ grains, containing an active substance. The only officinal ones are tablets of nitroglycerine, containing $\frac{1}{100}$th grain of pure nitroglycerine in each.

B.P.	DOSE.
Tabellæ Nitroglycerini	1 or two tablets.

Tincturæ. TINCTURES.—These are solutions of active principles in spirit. Rectified spirit, or alcohol, is used whenever the active principle is more soluble in strong than in dilute alcohol, as in the case of alkaloids, such as of veratrum viride; resins, such as asafœtida, benzoin, and Indian hemp; oils, such as those of cubebs, lavender, tolu, orange peel, larch bark, and ginger; and other substances, such as chloroform, acetate of iron, perchloride of iron, iodine, kino.

Aromatic spirit of ammonia is used in the ammoniated tincture of guaiac, of valerian, and of opium (B.P. and U.S.P.). In the case of guaiac and valerian the active principles have an acid character, and so ammonia tends to dissolve them more completely. In both of them, however, as well as in ammoniated tincture of opium, the ammonia has got a stimulating action of its own, which tends to aid the effect of the other substances.

Tinctures of fresh herbs (Tincturæ Herbarum recentium), when not otherwise directed, are, according to the U.S.P., to be prepared by macerating fifty parts of the fresh herb bruised or crushed in a hundred parts of alcohol for fourteen days, then expressing the liquid, and filtering.

B.P. (72).	DOSE.
	The usual dose is ½–2 fl. dr. unless otherwise mentioned.
Tinctura Aconiti	1–10 min.
,, Aloes	
,, Arnicæ	
,, Asafœtidæ	½–1 fluid drachm.
,, Aurantii	
,, ,, Recentis	
,, Belladonnæ	5–20 min.
,, Benzoini Composita	½–1 fluid drachm.
,, Buchu	
,, Calumbæ	
,, Camphoræ Composita	15 min.–1 fluid drachm.
,, Cannabis Indicæ	5–20 min.

B.P.	DOSE.
Tinctura Cantharidis	5–20 min.
„ Capsici	5–20 min.
„ Cardamomi Composita	
„ Cascarillæ	
„ Catechu	
„ Chiratæ	
„ Chloroformi Composita	10–60 min.
„ „ et Morphinæ	5–10 min.
„ Cimicifugæ	15–60 min.
„ Cinchonæ	
„ „ Composita	
„ Cinnamomi	
„ Cocci	
„ Colchici Seminum	10–30 min.
„ Conii	10–60 min.
„ Croci	
„ Cubebæ	
„ Digitalis	5–30 min.
„ Ergotæ	10–60 min.
„ Ferri Acetatis	5–30 min.
„ „ Perchloridi	5–30 min.
„ Gallæ	
„ Gelsemii	5–20 min.
„ Gentianæ Composita	
„ Guaiaci Ammoniata	½–1 fluid drachm.
„ Hyoscyami	½–1 fluid drachm.
„ Iodi	5–20 min.
„ Jaborandi	½–1 fluid drachm.
„ Jalapæ	
„ Kino	
„ Krameriæ	
„ Laricis	15–30 min.
„ Lavandulæ Composita	
„ Limonis	
„ Lobeliæ	10–30 min.
„ „ Ætherea	10–30 min.
„ Lupuli	
„ Myrrhæ	30–60 min.
„ Nucis Vomicæ	10–30 min.
„ Opii	5–40 min.
„ „ Ammoniata	30–60 min.
„ Podophylli	15–60 min.
„ Pyrethri	
„ Quassiæ	
„ Quininæ	
„ „ Ammoniata	
„ Rhei	(Stomachic) ½–2 fluid drachms.
„ „	(Purgative) 4–8 fluid drachms.
„ Sabinæ	10–60 min.
„ Scillæ	10–30 min.
„ Senegæ	
„ Sennæ	1 fluid drachm to 4 fluid oz.
„ Serpentariæ	
„ Stramonii	10–30 min.
„ Sumbul	10–30 min.
„ Tolutana	10–30 min. or more.
„ Valerianæ	
„ „ Ammoniata	½–1 drachm.
„ Veratri Viridis	5–20 min.
„ Zingiberis	10–60 min.
„ „ Fortior	5–20 min.

Tincture of Litmus, in Appendix, used as a test.

U.S.P. (73)	DOSE.
Tinctura Aconiti	1–3 m. (0·06–0·18 c.c.).
„ Aloes	(As laxative) ½–1 fl. dr.
„ „	(As purgative) 2–4 fl. dr.
„ „ et Myrrhæ	1–2 fl. dr. (3·75–7·5 c.c.).
„ Arnicæ Florum	10–30 m. (0·6–1·9 c.c.).
„ „ Radicis	20–30 m. (1·25–1·9 c.c.).
„ Asafœtidæ	30–60 m. (1·9–3·75 c.c.).
„ Aurantii Amari	1–2 fl. dr. (3·75–7·5 c.c.).
„ „ Dulcis	
„ Belladonnæ	15–30 m. (0·9–1·9 c.c.).
„ Benzoini	20–30 m. (1·25–1·9 c.c.).
„ „ Composita	½–2 fl. dr. (1·9–7·5 c.c.).
„ Bryoniæ	1–2 fl. dr. (3·75–7·5 c.c.).
„ Calendulæ	
„ Calumbæ	1–4 fl. dr. (3·75–15 c.c.).
„ Cannabis Indicæ	30 m. (1·9 c.c.).
„ Cantharidis	3–10 m. (0·07–0·30 c.c.).
„ Capsici	30–60 m. (1·9–3·7 c.c.).
„ Cardamomi	1 fl. dr. (3·75 c.c.).
„ „ Composita	1–2 fl. dr. (3·75–7·5 c.c.).
„ Catechu Composita	½–3 fl. dr. (1·9–11·25 c.c.).
„ Chiratæ	1–2 fl. dr. (3·75–7·5 c.c.).
„ Cimicifugæ	1–4 fl. dr. (3·75–15 c.c.).
„ Cinchonæ	1–4 fl. dr. (3·75–15 c.c.).
„ „ Composita	1–4 fl. dr. (3·75–15 c.c.).
„ Cinnamomi	1–4 fl. dr. (3·75–15 c.c.).
„ Colchici	½–2 fl. dr. (1·9–7·5 c.c.).
„ Conii	30 m. (1·9 c.c.) to be increased.
„ Croci	1–3 fl. dr. (3·75–11·25 c.c.).
„ Cubebæ	1–2 fl. dr. (3·75–7·5 c.c.).
„ Digitalis	10–20 m. (0·6–1·25 c.c.).
„ Ferri Acetatis	20–60 m. (1·25–3·75 c.c.).
„ „ Chloridi	10–30 m. (0·6–1·9 c.c.).
„ Gallæ	1–3 fl. dr. (3·75–11·25 c.c.).
„ Gelsemii	10–20 m. (0·6–1·25 c.c.).
„ Gentianæ Composita	1–2 fl. dr. (3·75–7·5 c.c.).
„ Guaiaci	1 fl. dr. (3·75 c.c.).
„ „ Ammoniata	1–2 fl. dr. (3·75–7·5 c.c.).
„ Herbarum Recentium	
„ Humuli	1–3 fl. dr. (3·75–11·25 c.c.).
„ Hydrastis	30–60 m. (1·9–3·75 c.c.).
„ Hyoscyami	60 m. (3·75 c.c.).
„ Ignatiæ	15–20 m. (0·9–1·25 c.c.).
„ Iodi	5–15 m. (0·3–0·9 c.c.).
„ Ipecacuanhæ et Opii	10 m. (0·6 c.c.).
„ Kino	1–2 fl. dr. (3·75–7·5 c.c.).
„ Krameriæ	1–2 fl. dr. (3·75–7·5 c.c.).
„ Lavandulæ Composita	30–60 m. (1·9–3·75 c.c.).
„ Lobeliæ	30–60 m. (1·9–3·75 c.c.).
„ Maticæ	1 fl. dr. (3·75 c.c.).
„ Moschi	½–2 fl. dr. (1·9–7·5 c.c.).
„ Myrrhæ	15–30 m. (0·9–1·9 c.c.).
„ Nucis Vomicæ	20 m. (1·25 c.c.).
„ Opii	11 m. (0·65 c.c.) or 22 drops.
„ „ Camphorata	1–4 fl. dr. (3·75–15 c.c.).
„ „ Deodorata	11 m. (0·65 c.c.).
„ Physostigmatis	20–40 m. (1·25–2·5 c.c.).
„ Pyrethri	
„ Quassiæ	1 fl. dr. (3·75 c.c.).
„ Rhei	1–2 fl. dr. (3·75–7·5 c.c.).
„ „ Aromatica	½–1 fl. dr. (1·9–3·75 c.c.).
„ „ Dulcis	2–3 fl. dr. (7·5–11·25 c.c.).
„ Sanguinariæ	30–60 m. (1·9–3·75 c.c.).

U.S.P.	DOSE.
Tinctura Saponis Viridis	
„ Scillæ	10–20 m. (0·6–1·25 c.c.).
„ Serpentariæ	1–4 fl. dr. (3·75–15 c.c.).
„ Stramonii	20–30 m. (1·25–1·9 c.c.).
„ Sumbul	20–60 m. (1·2–3·7 c.c.).
„ Tolutana	1–2 fl. dr. (3·75–7·5 c.c.).
„ Valerianæ	1–4 fl. dr. (3·75–15 c.c.).
„ „ Ammoniata	30–60 m. (1·9–3·75 c.c.).
„ Vanillæ	
„ Veratri Viridis	3–8 m. (0·18–0·5 c.c.).
„ Zingiberis	8–40 m. (0·5–2·5 c.c.).

U.S.P. **Triturationes.** TRITURATIONS.—These are intimate mixtures of substances with sugar of milk. Each contains 10 per cent. of the active substance. A general formula for their preparation is given in the U.S.P., although only one is named. According to this formula 10 parts of the substance and 90 parts of sugar of milk are to be weighed out separately. The substance, reduced to a moderately fine powder if necessary, is mixed in a mortar with about its own bulk of sugar of milk, and they are triturated together. Fresh portions of the sugar of milk are added from time to time until the whole has been added, and the trituration is continued until the substance is intimately mixed with the sugar of milk and finely comminuted.

U.S.P. Trituratio Elaterini.

Trochisci. LOZENGES.—These are small, flat, and hard, so that they can be readily carried about and melt slowly in the mouth. They are thus convenient for giving drugs which are intended to act upon the mouth or throat locally, or to be readily carried about and taken at times and in places where more bulky preparations would be inconvenient. Thus we have lozenges of chlorate of potassium, which are useful for soreness of the mouth and tongue; tannic acid and catechu, which are useful in relaxed sore-throat and hoarseness; ipecacuanha with morphine, and with opium, which are useful in coughs; bicarbonate of sodium useful before meals in dyspepsia or after meals in acidity; bismuth for irritability of the stomach; and reduced iron for debility. Bismuth, morphine, and opium are also useful in diarrhœa. In many cases it happens that although patients can take potions before, after, or with their morning and evening meals, they are unable to do so in the middle of the day when they are absent from home and engaged in various avocations. For such cases lozenges form a useful means of administering medicine.

B.P. (11).	U.S.P. (16)
Trochisci Acidi Tannici.	Trochisci Acidi Tannici.
„ Bismuthi.	„ Ammonii Chloridi.
„ Catechu.	„ Catechu.
„ Ferri Redacti.	„ Cretæ.
„ Ipecacuanhæ.	„ Cubebæ.
„ Morphinæ.	„ Ferri.
„ Morphinæ et Ipecacuanhæ.	„ Glycyrrhizæ et Opii.

B.P.	U.S.P.
Trochisci Opii.	Trochisci Ipecacuanhæ.
„ Potassii Chloratis.	„ Krameriæ.
„ Santonini.	„ Magnesiæ.
„ Sodii Bicarbonatis.	„ Menthæ Piperitæ.
	„ Morphinæ et Ipecacuanhæ.
	„ Potassii Chloratis.
	„ Sodii Bicarbonatis.
	„ „ Santoninatis.
	„ Zingiberis.

Unguenta. Ointments.—These are soft admixtures of medicines with fatty substances for external application. The basis of many of them is lard, either alone or mixed with benzoin in order to preserve it from rancidity, or mixed with white wax in the form of ointment (unguentum U.S.P.). In the B.P., simple ointment, which consists of white wax and almond oil, forms the basis of several ointments.

The semi-solid substances, obtained from American petroleum, form a useful basis for ointments, as they do not become rancid. They consist of hydrocarbons, mostly of the marsh-gas series. There are two chief varieties, one softer, having a melting point about 40° C. (104° F.), the other 51° C. (or 121° F.). They are obtained by distilling off the lighter and more volatile portions from American petroleum. They are known under different names, paraffin (B.P.), petrolātum (U.S.P.), unguentum petrolei, and vaseline.

B.P. (43).	U.S.P. (25).
Unguentum Acidi Borici.	Unguentum Acidi Carbolici.
„ „ Carbolici.	„ Acidi Gallici.
„ „ Salicylici.	„ „ Tannici.
„ Aconitinæ.	„ Aquæ Rosæ (cold cream).
„ Antimonii Tartarati.	„ Belladonnæ.
„ Atropinæ.	„ Chrysarobini.
„ Belladonnæ.	„ Diachylon.
„ Calaminæ.	„ Gallæ.
„ Cantharidis.	„ Hydrargyri.
„ Cetacei.	„ „ Ammoniati.
„ Chrysarobini.	„ „ Nitratis.
„ Creasoti.	„ „ Oxidi Flavi.
„ Elemi.	„ „ „ Rubri.
„ Eucalypti.	„ Iodi.
„ Gallæ.	„ Iodoformi.
„ „ cum Opio.	„ Mezerei.
„ Glycerini Plumbi Subacetatis.	„ Picis Liquidæ.
	„ Plumbi Carbonatis.
„ Hydrargyri (blue ointment).	„ „ Iodidi.
„ „ Ammoniati.	„ Potassii Iodidi.
„ „ Compositum.	„ Stramonii.
„ „ Iodidi Rubri.	„ Sulphuris.
„ „ Nitratis.	„ „ Alkalinum.
„ „ „ Dilutum.	„ Veratrinæ.
„ „ Oxidi Rubri.	„ Zinci Oxidi.
„ „ Subchloridi.	
„ Iodi.	
„ Iodoformi.	
„ Picis Liquidæ.	

B.P.	U.S.P.
Unguentum Plumbi Acetatis.	
,, ,, Carbonatis.	
,, ,, Iodidi.	
,, Potassæ Sulphuratæ.	
,, Potassii Iodidi.	
,, Resinæ.	
,, Sabinæ.	
,, Simplex.	
,, Staphisagriæ.	
,, Sulphuris.	
,, ,, Iodidi.	
,, Terebinthinæ.	
,, Veratrinæ.	
,, Zinci.	
,, ,, Oleati.	

B.P. Vapores. VAPOURS, INHALATIONS.—These are preparations for applying volatile drugs to the air-passages for the purpose of deodorising, disinfecting, stimulating or soothing. The drug is mixed with water and the vapour inhaled. If the drug be not readily volatile, warm water is used, as in the vapor creasoti, or the water is warmed during inhalation, as in the vapor iodi. In the vapor olei pini sylvestris, light carbonate of magnesium is added, to aid the suspension of the drug in the water.

B.P. (6).

Vapor Acidi Hydrocyanici	10 to 15 min. of the dilute acid to one drachm of cold water.
,, Chlori	2 oz. in cold water.
,, Coninæ	$\frac{1}{2}$ fluid oz. of succus to 1 oz. water and 1 drm. of liq. potassæ.
Creasoti	12 min. to 8 oz. of boiling water.
Iodi	1 drm. of tincture to the oz. of water.
,, Olei Pini Sylvestris	40 min. of fir-wool oil, 20 grs. magnes. carb.; water to 1 oz : 1 dr. in warm water, 1 pint as inhalation.

The vapours of chlorine, creasote, and iodine may be used for deodorising in cases of ozæna or in cases of chronic bronchitis with offensive sputa.

Antiseptic inhalations, such as those of creasote and iodine, as well as non-officinal inhalations of iodoform and oil of pine, have been recently used in the treatment of phthisis, with the object of destroying the tubercle bacillus. For this purpose a special form of inhaler is used, which fits over the mouth and nose. It contains a sponge which is soaked with the drug to be inhaled either pure or dissolved in spirit or water.

They are probably also useful even in simple catarrh, by destroying organisms which may have found their way into the air-passages and occasion or keep up inflammation. The vapours of hydrocyanic acid and conium are useful for the purpose of allaying irritability, as in spasm of the glottis, violent coughing, or spasmodic asthma.

Vina. WINES.—These are made in the same way as tinctures, sherry or orange wine (B.P.) or stronger white wine (U.S.P.) being employed instead of spirit.

B.P. (11)	DOSE.
Vinum Aloes	1–2 fluid drachms.
„ Antimoniale	5–30 min. as expectorant.
„ „	$\frac{1}{2}$–1 fluid oz. as emetic.
„ Aurantii	
„ Colchici	10–30 min.
„ Ferri	1–4 fluid drachms.
„ „ Citratis	1–4 fluid drachms.
„ Ipecacuanhæ	5–40 min. as expectorant.
„ „	1–8 drachms as emetic.
„ Opii	10–40 min.
„ Quininæ	$\frac{1}{2}$–1 fluid oz.
„ Rhei	1–2 drachms.
„ Xericum	

U.S.P. (14).	
Vinum Album	
„ Album Fortius	
„ Aloes	Stomachic, 1–2 drachms. Purgative, $\frac{1}{2}$–1 fluid oz.
„ Antimonii	Expectorant, 10–30 min.
„ Aromaticum	
„ Colchici Radicis	10 min.–1 fluid drachm.
„ „ Seminis	30 min.–2 fluid drachms.
„ Ergotæ	1–4 fluid drachms.
„ Ferri Amarum	2–4 fluid drachms.
„ „ Citratis	1–4 fluid drachms.
„ Ipecacuanhæ	Expectorant, 10–30 min. Emetic, 1–8 drachms.
„ Opii	15–20 min.
„ Rhei	1–4 fluid drachms.
„ Rubrum	

SECTION III.

INORGANIC MATERIA MEDICA.

CHAPTER XXII.

HYDROGEN, OXYGEN, OZONE, CARBON, SULPHUR, AND THE HALOGENS.

Although the officinal substances included in this chapter differ widely from each other in many respects, yet their relations to oxygen form a connecting link between them. Sulphur belongs to the same chemical group as oxygen. The chief action of charcoal is its power of oxidising organic substances by means of oxygen which it has condensed in its pores. The halogens probably owe their disinfecting properties in great measure to their power of liberating oxygen from water in the presence of organic matter which they thus oxidise and destroy.

HYDROGEN (H; 1). Not officinal.

Preparation.—By adding diluted hydrochloric or sulphuric acid to granulated zinc—

$$Zn + 2HCl = ZnCl_2 + H_2.$$

Uses.—It is of little or no use as a remedy, and is only used as a test.

It is very frequently employed in testing for arsenic, antimony, or sulphur. When in its nascent condition it has active chemical affinities, and readily unites with these substances, forming sulphuretted, arseniuretted, or antimoniuretted hydrogen.

OXYGEN (O; 16). Not officinal.

Properties.—Oxygen is a colourless gas without smell, slightly heavier than common air. It forms rather more than a fifth by volume of the atmosphere.

Preparation.—By heating chlorate of potassium with peroxide of manganese—

$$2KClO_3 = 2KCl + 3O_2.$$

Peroxide of manganese merely aids the decomposition of the chlorate of potassium, and takes no part in the reaction.

Physiological Action.—Oxygen applied to the unbroken skin has but little action, but when applied to a wound it increases

the circulation in it, and acts as a stimulant. When inhaled by healthy persons it causes a slight feeling of warmth in the mouth, extending downwards over the front of the body. In some people it appears to cause nervous symptoms somewhat like those produced by nitrous oxide.

In animals, excess of oxygen produces tetanic symptoms almost like those of strychnine, and death. This effect is produced by a pressure of three atmospheres, and it is evident that it is due to the oxygen and not to the simple increase in atmospheric pressure only, because when ordinary air is used, a pressure of three atmospheres has no such action, and a pressure of twenty-five atmospheres is requisite to produce this effect (Bert).

It has been thought by some that when oxygen has been once breathed it loses something which enables it to support life. The reason of this belief is that animals soon die which are kept in a confined space, from which the carbonic acid formed during respiration is absorbed by lime or baryta, and its place supplied by fresh oxygen. Professor Seegen, however, has found that the death in such cases is not due to the removal of anything from the oxygen, but to actual poisoning by the products of tissue-waste. In some experiments he noticed that the air in which the animal had been confined for a while, although its chemical composition was correct, had a disagreeable smell, and the animal after its removal soon died of pneumonia. When the air which the animal was breathing was extracted from one end of the compartment, made to pass through a red-hot tube, and introduced at the other end so that any organic matter formed during respiration was consumed, the animal could be kept for almost any length of time without injury to its health.

Uses.—Oxygen has been applied to the surface in atonic, scrofulous, and syphilitic ulcers, and in cases of senile or other gangrene. It has more especially been employed in cases of respiratory disease, such as emphysema, bronchial dilatation, phthisis, and gangrene of the lung, in asphyxia from noxious vapours or anæsthetics, and in spasmodic asthma. It seems to be chiefly of use in the latter disease. It has been employed also in cases of difficulty of breathing, of cardiac disease, and of anæmia from loss of blood or suppuration. It has been employed also in conditions where oxidation seems to be deficient, as in gout and diabetes, where sometimes the sugar disappears from the urine during its inhalation. Oxygen has also been used in the treatment of epilepsy and spasm.

It has been strongly recommended by Bert in paralysis occurring in divers, due to their sudden ascension from a great depth to the surface. When submerged at a considerable depth the pressure of the air causes both nitrogen and oxygen to be absorbed by the blood; when they return to the surface the oxygen enters into combination, but the nitrogen is set free in the blood-vessels,

forming minute bubbles, which act as emboli, obstructing the circulation in the nerve-centres and in the lungs, thus producing paralysis and dyspnœa. The nitrogen diffuses as readily into an atmosphere of oxygen as into an absolute vacuum; and therefore when animals, in which such a state has been artificially induced, have been made to breathe pure oxygen, bubbles of nitrogen disappear from the blood, the circulation is speedily restored to its normal condition, and the paralysis and dyspnœa disappear.

Its inhalation has been recommended in cases of cholera.

OZONE. Not officinal.

When an electric spark is passed through air a peculiar smell is noticed; this is due to the formation of ozone. The electricity in passing through the air appears to break up the molecules of ordinary oxygen (Fig. 164), and the atoms which are thus dis-

a *b*

FIG. 164.—Diagram to illustrate the formation of ozone by electricity. *a* represents oxygen, through which a spark is passing; *b* after it has passed. The double rings are intended to represent molecules of oxygen, each containing two atoms. As the electric spark passes through the oxygen it breaks up the first molecule, carrying one atom on to join the second molecule of oxygen, and form one of ozone. The atom which is left joins another molecule of oxygen, and also forms ozone. (After Lockyer.)

sociated join together so as to form ozone. It is also formed by the slow oxidation of phosphorus, and is formed also by protoplasm (p. 69). Two atoms are present in a molecule of oxygen and three in that of ozone. When electricity is passed through a quantity of oxygen, contained in a tube over mercury, so as to convert a portion of it into ozone, it becomes condensed in bulk and acquires much greater chemical activity. On warming it again to about 300° C. the molecules of ozone become again dissociated, ordinary oxygen is formed, the gas then returns to its original bulk, and it loses its active properties. Ozone has a most powerful oxidising property, attacking metals and forming oxides, and destroying organic substances, such as paper and caoutchouc. It has a curious action upon albumen, already described (p. 58), and decomposes blood. As might be expected,

it is exceedingly poisonous to low organisms, and is fatal also to the higher animals.

Its effect appears to be due in a great measure to its having such a powerful irritant and even destructive effect on the albuminous tissues of the respiratory passages, that it causes reflex depression of the heart and interferes with the ordinary respiration in the lungs. It thus diminishes instead of increasing oxidation. In animals it causes sometimes quickness, and sometimes slowness of the respiration (*vide* p. 241), and produces excitement followed by exhaustion and sometimes convulsions.

When it is present only in small quantity in air, it may be inhaled without any disagreeable effects, and is, according to Binz, a decided soporific.

Uses.—It has been recommended in cases similar to those already mentioned under oxygen; and also in infectious diseases, and in diphtheria, where it is likely to be useful by destroying low organisms, which produce the disease.

PEROXIDE OF HYDROGEN (H_2O_2; 34). Not officinal.

Properties.—When the watery solution thus obtained is evaporated it forms a transparent oily liquid; but it is generally employed in the form of a 3 per cent. solution (10 to 15 volumes) in water or in ether. The ethereal solution is commonly known by the name of ozonic ether; it is generally more stable than the aqueous solution, which, especially if kept in a badly stoppered bottle, soon decomposes into water and oxygen.

Preparation.—It is generally prepared by treating barium di-oxide with dilute sulphuric acid ($BaO_2 + H_2SO_4 = H_2O_2 + BaSO_4$) and filtering off the aqueous solution from the sulphate of barium which is precipitated.

Action and Uses.—Peroxide of hydrogen has a powerful oxidising effect upon organic substances, readily giving off an atom of oxygen in much the same way as ozone. It has therefore been used for similar purposes to ozone. It destroys bacteria, and is a powerful antiseptic.[1] When mixed with the secretion from a chancre it destroys its infective power; and it has been employed as a local dressing for chancres, and also as an application for diphtheritic sore-throat. Curiously enough, although when mixed with blood or with albumen it becomes decomposed almost immediately, it appears to be tolerably stable in the body, and is said to have been found in the urine after it has been taken by the mouth. By long-continued action upon egg-albumin, it is said to produce hemi-albumose and peptone.[2] Its internal administration has been recommended in rheumatism, scrofula, diabetes, and cardiac disease.

[1] Professor Dewar, Cambridge, unpublished experiments.

[2] Chandelon, Beitrag zum Studium der Peptonisation, *Ber. d. Deutsch. Chem. Ges.* XVII. p. 2143 (1885).

CARBON (C; 12).

This element is employed in medicine in the form of animal and vegetable charcoal.

Carbo Ligni, B.P. and U.S.P. WOOD CHARCOAL.—Wood charred by exposure to a red heat without access of air, B.P. Charcoal prepared from soft wood, U.S.P.

CHARACTERS.—In black, brittle, porous masses, without taste or smell, very light, and retaining the shape and texture of the wood from which it was obtained. When pulverised it forms a fine black powder.

PREPARATION.—It is prepared either by burning the wood under turf, or in retorts, so that the hydrogen and oxygen are driven off and charcoal alone remains. If too much air be allowed to have access, the charcoal itself becomes burnt, and too large a proportion of ash comes to be present.

IMPURITIES.—Too much ash.

TESTS.—When burned at a high temperature with free access of air it leaves not more than two per cent. of ash.

DOSE.—20–60 grains.

OFFICINAL PREPARATION.

B.P.	U.S.P.
Cataplasma Carbonis.	None.

B.P. Cataplasma Carbonis. CHARCOAL POULTICE.—Powdered charcoal 1; bread 4; linseed-meal 3; boiling water 20. Mix the water, bread, and linseed-meal, then add half the charcoal and sprinkle the remainder on the surface. By simply sprinkling a part of the charcoal on the surface of the poultice it is not wetted, and its disinfectant power not destroyed.

ACTION.—Charcoal has the power of absorbing gases and of condensing them within its pores. Amongst others it absorbs oxygen readily. The oxygen thus condensed has an oxidising action akin to that of ozone, and the charcoal parts with it readily when brought into contact with oxidisable substances, whether these substances be in solution or in the form of gas, but especially the latter. Thus it oxidises and decomposes sulphuretted hydrogen very readily, and also quickly oxidises and destroys decomposing organic substances. It thus acts as a deodoriser and disinfectant. It only possesses this power, however, when it is dry, and loses it when it is wet. For this reason the whole of it is not mixed with the poultice in the cataplasma carbonis, a part of it being merely sprinkled on the surface. Its oxidising power is destroyed completely only when the charcoal is thoroughly saturated with water, and this occurs with difficulty even when it is thrown into water. Consequently its oxidising power may still be exerted in fluids to which it has been freshly added.

USES.—It is employed as a deodoriser and disinfectant in traps through which sewer gases may pass, and in a respirator

for persons exposed to sewer gas or other noxious emanations. As a poultice it is employed for fœtid and phagedænic ulcers and gangrene. It forms a useful tooth-powder, cleaning the teeth rapidly, but it is much more apt to scratch the enamel than a tooth-powder of chalk. When taken into the stomach it relieves flatulent distension and acidity in the stomach and intestines. It has thus been used in acute and chronic dyspepsia, gastrodynia, and even cancer of the stomach; in constipation, flatulent distension of the colon, diarrhœa, dysentery, cancer of the rectum; it is recommended in drachm-doses by Sir William Jenner to correct flatulence and fœtid stools in typhoid fever. It has been supposed to relieve flatulence by absorbing the gases in the stomach and intestines, but as it will become wet by the juices of the intestinal canal after it is swallowed, it is much more probable that it acts mechanically, by removing mucus, or by stimulating the circulation and peristaltic movements in the walls of the stomach and intestine. This is rendered all the more probable by the fact that in some cases where it is useful the patient is likewise benefited by beginning each meal with solid food, and abstaining from liquids until the meal is well over, so that the stomach may receive a mechanical stimulus from the food, which would be prevented by the ingestion of much liquid at the beginning of the meal. In large doses it acts as a mild purgative. It has also been used in diabetes and in intermittent fevers.

ADMINISTRATION.—It is either used in the form of powder, or made up into biscuits or lozenges.

Carbo Animalis, B.P. and U.S.P. ANIMAL CHARCOAL.—Bone black. Animal charcoal prepared from bone, U.S.P. The residue of bones which have been exposed to a red heat without the access of air. Consists principally of carbon and phosphate and carbonate of calcium, B.P.

Carbo Animalis Purificatus, B.P. and U.S.P. PURIFIED ANIMAL CHARCOAL.

CHARACTERS.—It is a black powder without taste or smell. It absorbs colouring matters, and tincture of litmus diluted with 20 times its bulk of water agitated with it and thrown upon a filter passes through colourless. It is insoluble in all reagents.

PREPARATION.—By dissolving out the earthy matter by hydrochloric acid, washing and drying.

IMPURITIES.—Too much ash.

TEST.—When burnt at a high temperature with a little red oxide of mercury and free access of air, it leaves only a slight residue.

DOSE.—20–60 grains.

USES.—From its power of absorbing colouring matters, animal charcoal is used in the preparation of organic alkaloids, for the purpose of decolorising them. It not only carries down

colouring matters with it, but alkaloids as well, and therefore a considerable loss is occasioned in the process of bleaching. Advantage has been taken of this power to use animal charcoal as an antidote in poisoning by opium, aconite, nux vomica, &c. The alkaloid is removed from solution by the animal charcoal and retained by it with considerable pertinacity. It would, however, be gradually dissolved out if allowed to remain too long in the stomach, and therefore the stomach-pump, or emetics, must be used in addition. As an antidote it is used in doses of a tablespoonful frequently repeated.

SULPHUR (S; 32).

Sulphur is found native in volcanic districts, and occurs in combination with metals as sulphites in various ores, especially in iron and copper pyrites.

Sulphur Sublimatum, B.P. and U.S.P. SUBLIMED SULPHUR, FLOWERS OF SULPHUR.

CHARACTERS.—A fine, slightly gritty, citron-yellow or greenish-yellow powder, without taste or smell unless heated. It may sometimes have a slight characteristic odour, a faintly acid taste and an acid reaction from slight oxidation occurring with the formation of small quantities of sulphurous acid.

SOLUBILITY.—It is insoluble in water or alcohol, slightly soluble in oils and fats, and completely soluble in carbon disulphide.

REACTION.—When ignited it burns with a blue flame, forming sulphurous acid gas, and leaving no residue, or only a trace.

PREPARATION.—By sublimation from crude or rough sulphur. Native sulphur is usually mixed with earthy impurities. When heated the sulphur volatilises. If the vapour is condensed in a large room it falls in a fine powder. If condensed in water it forms masses, which, when melted and run into moulds form roll sulphur, but this is not officinal. Ores containing sulphur are decomposed by heat, and part of the sulphur they contain sublimes, and may be condensed in the same way as native sulphur.

IMPURITIES.—Ores are apt to contain arsenic, and when this is the case sulphide of arsenic, being volatile, sublimes along with the sulphur and renders it impure. During sublimation the sulphur may undergo oxidation, and thus sulphurous or sulphuric acid may be present in it as impurities.

TESTS.—*Vide* SULPHUR LOTUM.

OFFICINAL PREPARATIONS.

B.P.	DOSE.	U.S.P.
Confectio Sulphuris, as laxative	60–120 gr.	Sulphur Lotum.
„ „ as alterative	5–20 gr.	„ Præcipitatum.
Emplastrum Ammoniaci cum Hydrargyro.		
„ **Hydrargyri.**		
Pulvis Glycyrrhizæ Compositus (1 in 12)	30 to 60 gr.	
Unguentum Sulphuris.		Unguentum Sulphuris.

Used in preparing:
Antimonium Sulphuratum.
Potassa Sulphurata.
Sulphuris Iodidum.
Sulphur Præcipitatum.

B.P. Confectio Sulphuris. CONFECTION OF SULPHUR.—Sulphur 4; acid tartrate of potassium 1; syrup of orange-peel 4; tragacanth in powder $\frac{1}{24}$ part. The acid tartrate of potassium is added for the purpose of increasing the secretion from the intestine, while the sulphur stimulates peristaltic action.

Unguentum Sulphuris. SULPHUR OINTMENT.—Sulphur mixed with benzoated lard, 1 part to 4, B.P.; 30 to 70, U.S.P. The U.S.P. ointment is nearly twice as strong as the B.P.

USES.—See pp. 546, 547.

In **skin diseases** sulphur is used both as an **antiparasitic**, and as a **stimulant** in chronic and passive congestion. It is used as an ointment in scabies, and in tinea tonsurans, in severe cases of which an ointment of sulphur and tar with soap may be used, four drachms of sulphur and oil of cade to one ounce each of green soap and lard. In the true prurigo of Hebra it may be employed in Vleminckx's solution, which is made according to the following formula:—

℞ Calcis ....℥ss.
Sulphuris Sublimati..................℥j.
Aquæ ....℥x.
Evaporate to ℥vj., then filter.

The solution must be rubbed into the skin while the patient is in a bath at the temperature of the body (98° F.). Obstinate cases of psoriasis may be similarly treated. Unguentum sulphuris is useful in acne, sycosis, seborrhœa, and chronic indurated eczema. In lupus erythematosus and lupus attended with a congested condition of the scalp, a paste of alcohol and sulphur is recommended.

U.S.P. Sulphur Lotum. WASHED SULPHUR.

CHARACTERS AND IMPURITIES.—Those of sulphur sublimatum.

PREPARATION.—By digesting sulphur with dilute ammonia, thoroughly washing, drying at a gentle heat, and passing through a No. 30 sieve. In this process the ammonia not only neutralises any sulphurous or sulphuric acid, but dissolves out and removes sulphide of arsenic which may be present in the sulphur, and which is soluble in ammonia.

TESTS.—Water agitated with it should not redden blue litmus paper (absence of free acid). If washed sulphur be digested with two parts of water of ammonia, and the mixture filtered, the filtrate, on being supersaturated with hydrochloric acid, should remain unaltered (absence of arsenious sulphide), nor should a precipitate make its appearance on passing hydrosulphuric acid through the filtrate (absence of arsenious acid).

OFFICINAL PREPARATIONS.

U.S.P.

Pulvis Glycyrrhizæ Compositus. (1 in 12½.)
Sulphuris Iodidum.
Unguentum Sulphuris Alkalinum.

U.S.P. Unguentum Sulphuris Alkalinum. ALKALINE SULPHUR OINTMENT. Sulphur 20; carbonate of potassium 10; water 5; benzoated lard 65.

Sulphur Præcipitatum, B.P. and U.S.P. PRECIPITATED SULPHUR, LAC SULPHURIS, MILK OF SULPHUR.

CHARACTERS.—Being in a finer state of division than sublimed sulphur, it looks almost white, with only a slight tinge of yellow. Otherwise its characters are the same.

PREPARATION.—By boiling sulphur with slaked lime and water. Calcium sulphide and calcium hyposulphite are thus formed.

$$3CaO + 6S_2 = 2CaS_5 + CaS_2O_3.$$

These dissolve in water, and are separated from any residual lime by filtration. To the filtrate, in an open space or under a chimney, hydrochloric acid is then added, which decomposes these substances with the evolution of sulphuretted hydrogen and sulphurous acid gases, and throws down sulphur in the form of an exceedingly fine powder, which is washed until the washings are tasteless (U.S.P.) and have no acid reaction and cease to give a precipitate with oxalic acid (B.P.), showing that both acid and lime have been removed.

IMPURITIES.—There is a great temptation to fraudulent manufacturers to use sulphuric acid instead of hydrochloric acid. It is not only cheaper but it yields a large product, consisting to a great extent of sulphate of calcium, which is precipitated along with the sulphur instead of remaining in solution like the calcium chloride which is formed when hydrochloric acid is employed.

With Hydrochloric acid, $CaS_5 + 2CaS_2O_3 + 6HCl = 3S_2 + 2H_2O + H_2S + 2SO_2 + 3CaCl_2$.

With Sulphuric acid, $CaS_5 + 2CaS_2O_3 + 3H_2SO_4 = 3S_2 + 2H_2O + H_2S + 2SO_2 + 3CaSO_4$.

Besides this there are the other impurities which may be present in the sublimed sulphur employed in the process.

TESTS.—It should be completely volatilised by heat and leave no residue of sulphate behind. Under the microscope it should exhibit only minute globules of sulphur and no crystals of sulphate. The absence of the impurities contained in sublimed sulphur is ascertained by the tests already given.

DOSE.—Of precipitated sulphur, as alterative 10 grs., as laxative 30–60 grs.

Sulphuretted Hydrogen. HYDROGEN SULPHIDE. (H_2S; 34.) A colourless gas, with a smell of rotten eggs. Used only as a test.

PROPERTIES.—It precipitates most metals as sulphides from acid solutions, the precipitate with arsenic being yellow; antimony, orange; cadmium, yellow; copper, lead, mercury, and silver, black; bismuth, brown; gold and platinum, brownish black.

PREPARATION.—By pouring diluted sulphuric acid on sulphide of iron. By passing the gas into cold water a solution is obtained.

General Action of Sulphuretted Hydrogen.—As sulphuretted hydrogen is formed in small quantities from sulphur when the latter is used in various ways, it may be more convenient to take its action before that of sulphur. It is very destructive to plant life even in very minute quantities. There is a curious

difference between the action of sulphuretted hydrogen and that of sulphurous acid on plants. The latter seems to act as an irritant, causing the leaves to crumple up and fall off, but even when the leaves are destroyed by sulphurous acid the plant may again recover. Sulphuretted hydrogen causes the leaves simply to become flaccid and droop, but when this has once taken place the plant does not recover.

In animals it destroys the functions of all tissues, and in consequence has two actions which are well marked, (1) decomposing the **blood** and thus producing symptoms of asphyxia, and (2) paralysing the **nervous system** and **muscles.** It is **absorbed** by the skin, by the lungs, mucous membrane of the alimentary canal, and subcutaneous cellular tissue, and may produce symptoms of poisoning through any of these channels. In **frogs**, which are less affected than mammals by interference with the respiration, the symptoms produced by sulphuretted hydrogen are those of paralysis of voluntary motion and reflex action, preceded by a stage of restlessness. In **mammals** the symptoms are those of asphyxia; muscular tremors occur, and are succeeded by asphyxial convulsions and death. Most cases of poisoning by sulphuretted hydrogen in man occur from inhalation of the gas which is often found in large quantities in cesspools.

One case has been recorded where symptoms of poisoning occurred from the excessive formation of the gas in the intestinal canal, and subsequent absorption into the blood. Cases of poisoning are best treated by artificial respiration.

Special Action.—Even in minute quantities it destroys the catalytic action of many substances on peroxide of hydrogen. In this respect, as well as in many of the symptoms it produces, it resembles hydrocyanic acid.

On the **blood.** It first reduces and then decomposes hæmoglobin. Both the blood and the muscles of frogs poisoned by it exhibit a greenish colour. As death occurs in mammals before the blood has become so extensively changed, it simply exhibits the characters of asphyxial blood. It induces rigor mortis rapidly in the **muscular substance** both of the voluntary muscles and of the frog's heart.

Action of Sulphur.—Sulphur, when brought into contact with living **protoplasm,** enters into combination and forms sulphuretted hydrogen or sulphurous acid. When sulphur is sprinkled over actively-growing fungi, like those which cause the vine-disease, these gases are formed and the fungi destroyed.

Sulphur has little or no action on the **skin,** excepting a mechanical one. It is a **laxative** (p. 394). When taken into the **intestinal canal,** a considerable part of it again passes out unchanged; a little of it, however, appears to be converted into sulphides and into sulphuretted hydrogen. The latter is **excreted**

by the breath, and may give to it the peculiar disagreeable smell of rotten eggs. It is also excreted by the skin, so as to blacken any silver articles which may be worn about the person. The sulphides give rise to increased peristaltic action of the bowels, so that the motions become more frequent and softer; colicky pains are sometimes produced. The sulphides, after absorption into the blood, are excreted in the urine, chiefly as sulphates.

Uses.—For its use in skin disease, *vide* p. 544. It has been applied by insufflation to the throat in diphtheria, in order to destroy the organisms present in the pharynx, in the same way as in the vine-disease. I have seen one case do very well under this treatment; but its general efficacy is by no means certain. Internally it is employed as a mild laxative in cases of constipation where active purgatives are inadmissible, as in pregnancy, in hæmorrhoids, fissure of the anus, and stricture or prolapsus of the rectum. It has been used also in cases of lead-poisoning, to prevent the reabsorption of the lead from the intestine.

It has been found useful in cases of sexual irritation arising from hæmorrhoidal congestion (p. 451), and also in the nervous excitement and other disturbances accompanying the menopause.

It exerts a beneficial action on the tissues in chronic rheumatism and gout, and is especially useful in the form of sulphurous waters. During its elimination by the lungs it is supposed to have a beneficial action on them, and it is consequently used in chronic bronchitis.

HALOGEN ELEMENTS.

Fluorine (Fl; 19 or 19·1). **Chlorine** (Cl; 35·5 or 35·4).
Bromine (Br; 80 or 79·75). **Iodine** (I; 127 or 126·53).

These substances form a series in which the atomic weights are nearly in the relation of 1, 2, 4, and 7 (*vide* also p. 16). They are distinguished by the activity of their chemical affinities and the number of compounds they form.

General Source.—The name halogen (from ἅλs, the sea) has been given to the group, because its most important members, chlorine, bromine, and iodine, are derived from the sea; chlorine being obtained from sea-salt, bromine from sea-water, iodine from sea-weed.

General Characters.—They are all very volatile. At ordinary temperatures, chlorine is a gas, bromine a liquid, and iodine a solid, but both bromine and iodine give off vapour freely. On account of their active chemical affinities they unite directly with metals, as is seen in the officinal processes for the preparation of iodide of iron and green iodide of mercury. They have

all a great affinity for hydrogen, and are therefore powerful decomposers of organic matter, destroying organic colours and disagreeable emanations of organic origin, as well as decomposing sulphuretted hydrogen ($H_2S + Cl_2 = 2HCl + S_2$) and ammonia which occur amongst the products of decomposition of organic matter. They are therefore used as deodorisers and disinfectants. Chlorine is used for bleaching, but bromine and iodine form coloured compounds with many organic substances, and so are not used for this purpose.

Probably the bleaching power of chlorine is not due to its decomposing organic colours by removing hydrogen from them, but rather to its decomposing water by removing the hydrogen from it, and thus setting free nascent oxygen, which is the direct destroyer of organic matters. The reason for this supposition is that chlorine does not act upon colouring matters when they are dry, but only when moist.

Mode of Preparation.—Chlorine, bromine, and iodine are all prepared by expelling them from their compounds with the alkaline metals by means of sulphuric acid and manganese dioxide.

Chlorine is prepared by putting sodium chloride, sulphuric acid and manganese dioxide into a retort, applying heat and collecting the chlorine gas in a receiver, by displacement or over warm water, or passing it into cold water which dissolves it freely, forming liquor chlori (B.P.) or aqua chlori (U.S.P.).

Bromine is prepared in a similar manner from the bromides of sodium and magnesium contained in the bittern or mother-liquor left after the salt has crystallised out of sea-water or out of the brine obtained in salt mines. In order to obtain the bromine pure, the bittern is often not treated directly with sulphuric acid and manganese dioxide. Instead of this the bromine is first separated by passing chlorine through the liquid, which is then shaken up with ether. The chlorine decomposes the magnesium bromide and the ether dissolves the bromine thus set free. The bromine is then converted again by potash into bromide, from which bromine is obtained by means of manganese dioxide and acid.

Iodine is prepared in a similar manner to chlorine from the iodides of sodium and magnesium contained in sea-weed. The iodides are obtained from the weed by calcining it in a retort, or by burning it, when the ashes in which they are contained form a hard mass called kelp. This is treated with successive portions of water until the soluble salts are all dissolved out (lixiviation). The solution is filtered, and evaporated to a small bulk, when the less soluble salts, as the sulphates, &c., crystallise out. The mother-liquor containing the iodides of sodium and magnesium is then treated with manganese dioxide and sulphuric acid, and the iodine distils over.

The reactions which occur in the preparations just described are—

Chlorine	$2NaCl + 2H_2SO_4 + MnO_2 = Cl_2 + Na_2SO_4 + MnSO_4 + 2H_2O.$
Bromine	$2NaBr + 2H_2SO_4 + MnO_2 = Br_2 + Na_2SO_4 + MnSO_4 + 2H_2O.$
	$MgBr_2 + 2H_2SO_4 + MnO_2 = Br_2 + MgSO_4 + MnSO_4 + 2H_2O.$
Iodine	$2NaI + 2H_2SO_4 + MnO_2 = I_2 + Na_2SO_4 + MnSO_4 + 2H_2O.$
	$MgI_2 + 2H_2SO_4 + MnO_2 = I_2 + MgSO_4 + MnSO_4 + 2H_2O.$

General Action.—As chlorine, bromine, and iodine decompose organic compounds having a disagreeable odour, they have been supposed to have a similar action upon the germs of infectious diseases. Chlorine, and sometimes iodine, are therefore used as **deodorisers** and **disinfectants** in sick rooms. Bromine cannot well be used on account of its abominable smell.

The objections to chlorine or the vapour of iodine as disinfectants are that we do not at all know that they have any disinfecting power in the dilute state, in which only they can be used in a sick room. When applied to the **skin** or mucous membranes they cause a greater or less amount of irritation or inflammation, according to the length of time during which they act, and the greater or less degree of concentration in which they are applied. They probably do not enter the blood in the free state, but combine with bases or with albuminous substances at the place of application, and are **absorbed** as chlorides, bromides, or iodides, or else as albuminous compounds. According to Binz, free chlorine, bromine, and iodine, and all their readily decomposable compounds, have a narcotic action, and paralyse nervous centres in the brain by a direct action on the nervous structures themselves. He considers that they cause death by paralysis of the respiratory centre, and not by paralysis of the heart.

CHLORINE. Cl; 35·5.

A greenish-yellow gas with a suffocating odour. Its preparation and general action have already been described (p. 548).

Action.—When applied for a long time to the **skin**, as in persons who have to work in an atmosphere containing it, it causes itching, reddening, and inflammation. When applied to the more sensitive **mucous membranes** of the respiratory passages, it acts as a stimulant or irritant. In a concentrated form it may cause death from spasm of the glottis, or intense bronchitis. In a more dilute form it is used as a stimulant, deodoriser, and **disinfectant**. The manner of employing it is to put a saucer containing salt, binoxide of manganese, and sulphuric acid on a shelf or high piece of furniture in the sick room, and thus allow the chlorine vapour, which is heavier than air, to diffuse itself through the apartment. When placed on the floor it is of little use.

Liquor Chlori, B.P.; Aqua Chlori, U.S.P. Chlorine Water.—An aqueous solution of chlorine containing at least 0·4 per cent. of the gas U.S.P., or 2·66 grains in 1 fluid ounce = about 0·6 per cent. B.P.

Characters.—A greenish-yellow clear liquid with a strong smell and taste of chlorine. It instantly decolorises dilute solutions of litmus and indigo.

Preparation.—By passing washed chlorine into water (p. 548). The chlorine is directed by the B. and U.S.P. to be prepared from hydrochloric acid and manganese dioxide, instead of from sodium chloride. $4HCl + MnO_2 = Cl_2 + MnCl_2 + 2H_2O$.

Impurities.—The chief is too little chlorine. When exposed to light it is apt to be decomposed, the chlorine combining with the hydrogen of the water and forming hydrochloric acid. The chlorine water thus loses strength, and it also becomes weaker by the chlorine escaping when the bottle is imperfectly stoppered or frequently opened. A solution of chlorinated soda or lime may be sometimes substituted for chlorine water.

Tests.—The amount of chlorine is not tested directly but indirectly, by estimating the amount of iodine which a definite quantity of chlorine water liberates from iodide of potassium. In this process, chlorine water (439 grains or 1 fluid ounce B.P., or 35·4 gm. U.S.P.) is mixed with iodide of potassium (20 grains B.P., 0·9 gm. U.S.P.) and water (1 fluid ounce B.P., 20 gm. U.S.P.). The amount of iodine which is set free by the chlorine ($2KI + Cl_2 = 2KCl + I_2$) gives a red colour to the solution, and corresponds in quantity to the chlorine contained in the water. The red solution requires for its decolorisation 750 grain-measures B.P., or 40 cc. U.S.P. of the volumetric solution of hyposulphite of sodium. The reaction which occurs is :—

Iodine.		Sodium Hyposulphite.		Sodium Iodide.		Sodium Tetrathionate.		Water.
I_2	+	$2Na_2H_2S_2O_4$	=	$2NaI$	+	$Na_2S_4O_6$	+	$2H_2O$.

Uses.—Chlorine is used in solution as a lotion to foul-smelling ulcers or cancer; as an application to relieve itching in chronic skin diseases; and as a gargle or wash to the mouth in affections of the mouth, throat, and tonsils, especially where they are accompanied by fœtor, as in mercurial ptyalism and ulceration of the tonsils. It is sometimes given internally in cases of blood-poisoning. As an inhalation it has been used in cases of phthisis, it is said with good effect. It is also employed as a stimulant and deodoriser in cases of chronic bronchitis with fœtid sputa. (*Vide* Vapor Chlori, p. 533.)

The aqueous solution is so unstable and liable to lose its strength, that compounds of chlorine from which it can be easily evolved are more convenient for general use. The chief of these are the following compounds with lime and with soda.

Calx Chlorinata, B.P.; Calx Chlorata, U.S.P. Chlorinated Lime.—A product obtained by exposing slaked lime to the action of chlorine gas so long as the latter is absorbed. It possesses bleaching and disinfecting properties. It may be regarded as consisting, chiefly, of a compound of hypochlorite and chloride of calcium ($CaCl_2O_2,CaCl_2$) or as a direct compound of chlorine and

lime, B.P. A compound resulting from the action of chlorine upon hydrate of calcium, and containing at least 25 per cent. of available chlorine, U.S.P.

CHARACTERS.—A greyish-white powder having the odour of chlorine and an acrid taste; it absorbs carbonic acid and water when exposed to the air, and at the same time gives off chlorine; it is only partly soluble in water. The solution is alkaline, and possesses bleaching properties (e.g. it bleaches sulphate of indigo).

It is readily decomposed by acids, even by carbonic acid, and thus when exposed to the air chlorine is given off slowly. The addition of a stronger acid causes it to be evolved rapidly. Its probable constitution is $Ca\left\{\begin{matrix}Cl.\\OCl.\end{matrix}\right.$ This is decomposed by water into a mixture of calcium chloride and hypochlorite, and as it is usually moist it may be regarded as usually consisting of a mixture of these substances. On the addition of sulphuric acid, hypochlorous and hydrochloric acids are set free, which reacting on one another yield free chlorine. $HClO + HCl = Cl_2 + H_2O$.

REACTION.—The addition of oxalic acid causes the rapid and copious evolution of chlorine and the deposition of oxalate of calcium.

IMPURITIES.—Imperfect saturation with chlorine. It is tested volumetrically in a similar way to liquor chlori, the chlorine being set free from it by the addition of hydrochloric acid. The chlorine thus liberated should amount to 30 per cent. B.P., 25 per cent. U.S.P.

OFFICINAL PREPARATIONS.

B.P.	U.S.P.
Liquor Calcis Chlorinatæ.	Liquor Calcis Chloratæ.
Vapor Chlori (p. 533).	

Chlorinated lime is used in the preparation of Chloroform.

Liquor Calcis Chlorinatæ. SOLUTION OF CHLORINATED LIME.—It is a solution of 1 lb. to the gallon of water, and when tested volumetrically it should contain 13 grains of available chlorine in 1 fluid oz.

Liquor Sodæ Chlorinatæ, B.P.; Liquor Sodæ Chloratæ, U.S.P. SOLUTION OF CHLORINATED SODA.—(Labarraque's disinfecting fluid.)

CHARACTERS.—A colourless alkaline liquid, with astringent taste and feeble odour of chlorine.

PREPARATION.—By passing chlorine into a solution of sodium carbonate B.P., or by decomposing chlorinated lime by sodium carbonate U.S.P.

TESTS.—It behaves like a solution of chlorinated lime, but is not precipitated by oxalic acid nor oxalate of ammonium. (Distinction from and absence of solution of chlorinated lime.)

DOSE.—10 to 20 minims.

OFFICINAL PREPARATION, B.P.

Cataplasma Sodæ Chlorinatæ.

Cataplasma Sodæ Chlorinatæ.—Linseed meal 2; solution of chlorinated soda 1; boiling water 4.

Uses.—Chlorinated lime is chiefly employed as a disinfectant and a deodoriser. In sick rooms some of it is put in saucers, and, according to the rapidity with which the evolution of chlorine is desired, either acid is added to it, or it is simply moistened and exposed to the air, when it is slowly decomposed by the carbonic acid. It is employed also for disinfecting typhoid stools, water-closets, and sewers. For this purpose it is used either in powder or solution. A solution is used to disinfect the sheets and bedding of patients suffering from infectious diseases.

Solutions of chlorinated lime or of chlorinated soda may be employed instead of chlorine water or permanganate of potassium for washing the hands after dissecting or performing *post-mortem* examinations. They are applied externally to wounds and ulcers of all sorts which have a fœtid discharge and a tendency to slough. Not only do they remove the fœtor, but they often induce a healthy action in the tissues themselves; and instead of the ulceration or sloughing extending farther and farther, the slough is thrown off and leaves behind it a healthy, healing surface. As the removal of sloughs is aided by heat, we have in the B.P. the poultice of chlorinated soda.

Like chlorine they are destructive to plant life, and they are therefore useful in skin-diseases depending on the presence of parasitic fungi, such as ringworm of the scalp, and in scabies which is due to the presence of a parasitic acarus. As they have a stimulant action on the skin, they are sometimes useful in eczema and prurigo.

They are employed as gargles, or washes to the mouth when fœtid ulcers occur in these parts, as in ptyalism or in scarlatina; as an injection into the nose they have been used to lessen the discharge and to remove the fœtor in ozæna, a disease in which the discharge from the nostrils is sometimes so disgusting as to be almost unendurable to the patient himself as well as to those around him. They are likewise useful in fœtid discharges from the vagina, such as occur when the uterus is the seat of malignant disease.

Internally they have been employed in so-called putrid fevers, when it was imagined there was a special tendency to decomposition in the blood, such as typhus and malignant scarlatina. They have been given more especially in these diseases when there was great prostration of strength, with fœtid evacuations and a dry and furred tongue.

BROMUM. Br; 80.

Bromine, B. and U.S.P. A liquid non-metallic element obtained from sea-water and from some saline springs.

Characters.—A dark brownish-red, very volatile liquid, with

a strong, disagreeable odour. The solution renders cold starch-water yellow.

PREPARATION.—*Vide* p. 548.

IMPURITY.—Iodine.

TEST.—When agitated with sufficient soda to render the fluid very slightly alkaline, it forms a colourless liquid, which, if coloured by a further addition of a little bromine, does not become blue on the subsequent addition of a cold solution of starch. B.P. (absence of iodine).

If an aqueous solution of bromine be poured upon reduced iron and shaken with the latter until it has become nearly colourless, then filtered, mixed with gelatinised starch, and a few drops of bromine solution be now carefully poured on the top, not more than a very faint blue zone should appear at the line of contact of the two liquids (limit of iodine), U.S.P.

USES.—Bromine, although a powerful **disinfectant**, is not much used, on account of its exceedingly fœtid and disagreeable smell. It is a powerful irritant, and when inhaled without sufficient dilution with air will produce pneumonia. Taken in small doses, for a length of time, it has produced mental depression, drowsiness, and stupidity. It is sometimes used as a caustic to the os uteri, and from its deodorising and antiseptic action it is especially useful where there is a fœtid discharge. It is used internally in the form of its potassium, sodium, ammonium, calcium, and zinc salts, and of hydrobromic acid, which do not possess its powerfully irritant local action.

Potassii Bromidum, B. and U.S.P. BROMIDE OF POTASSIUM. (KBr; 118·75.)

CHARACTERS.—In colourless cubical crystals, with no odour, but a pungent saline taste.

PREPARATION.—*Vide* p. 605.

SOLUBILITY.—It is readily soluble in water, less soluble in spirit.

REACTIONS.—Its aqueous solution gives the reactions of potassium (p. 603) and a bromide (p. 594).

IMPURITIES.—Iodide and bromate.

TEST.—For the iodide, *vide* p. 560. Bromate is detected by adding dilute sulphuric acid to the crushed crystals. They should not at once assume a yellow colour. The acid liberates hydrobromic acid from the bromide, and if bromate be present the reaction between it and the hydrobromic acid liberates free bromine. $5HBr + HBrO_3 = 3H_2O + 3Br_2$.

ACTION.—Bromide of potassium does not seem to have, like the iodide, any marked influence on the lymphatic system, and although it has been occasionally used instead of the iodide in lymphatic swellings and enlargements of organs, this use of it is not general. When swallowed in small doses it produces no effect, but when taken in **large doses** for a considerable time it causes an eruption like acne upon the face, the complexion at the same time becoming muddy or bronzed. The chief symptoms are, however, impairment of the functions of the **spinal cord** and the **brain**. There is a great diminution of reflex action, so that touching the pharynx no longer produces any tendency to vomit,

even though the touch itself be felt. There is drowsiness and heaviness, a great inclination to sleep and insensibility to outward impressions, the memory is impaired, the speech becomes hesitating and articulation imperfect, the intellect is less clear, the genital functions are much diminished, the gait becomes tottering and unsteady, and the muscles weak. To these symptoms the name of **bromism** is given.

Uses.—Its chief use is in **nervous diseases** for the purpose of producing sleep, allaying excitement, and diminishing spasm.

Bromide of potassium is most useful as a **hypnotic** in cases of sleeplessness due to mental excitement and worry. Some persons, after hard study or close attention to business, instead of sleeping at night are no sooner in bed than the brain seems to become doubly active, the carotids throb and they toss about from side to side trying in vain to get rid of the ideas which come in a constant train before them. In such cases when bromide of potassium is taken, the throbbing of the carotids and temporals and the fulness in the head disappear and sleep is induced. A dose of 10–15 grains given before bed-time may be sufficient in mild cases, but when the agitation is great 30 or 40 grains must be given, and should be assisted by cold ablution to the head and a prolonged warm foot-bath. The dose may be repeated, if necessary, every hour or two hours, until the desired effect has been obtained. One great advantage that bromide of potassium possesses over other hypnotics is that it can be pushed without fear, and the same is true of other bromides. They are not dangerous to life, and even when they are pushed so far as to cause bromism, the symptoms usually pass off rapidly when the drug is discontinued.

It is very useful in lessening the excitability, susceptibility to worry, and **irritability** of temper from which gouty persons often suffer. It should be given with a considerable proportion of water.

In delirium tremens where there is sleeplessness with fearful visions it may be given in doses from 20–30 grains or even more every two hours till sleep is induced. It is of most benefit in the earlier stages before the delirium has become furious, and is useful also at the end of the attack in dispelling delusions which may still remain.

During the latter months of pregnancy, women are sometimes troubled at night with the imagination that they have committed or are about to commit some great crime, such as murdering their husbands or children; and these delusions, according to Ringer, are removed by potassium bromide.

It is also useful, he says, in the treatment of night screaming in children, apparently allied to nightmare. They awake out of sleep screaming, seem very much frightened, and do not appear to recognise their mother or other friends who try in

vain to soothe them. In the sleeplessness of mania it is frequently though not always successful. It may be used in fevers and inflammation when sleep is absent, and whenever opium and belladonna or hyoscyamus fail to produce sleep or cause sickness.

In **convulsive nervous affections**, such as whooping cough, laryngismus stridulus and spasmodic asthma, it is very useful, and also to some extent in St. Vitus's dance and hysteria.

It is especially beneficial in **epilepsy**, and by its use the convulsions can almost always be lessened if not entirely stopped. A similar result has been obtained in experiments on animals (p. 187). It is not so useful when the convulsions are violent, and it is not so beneficial when there is only a transitory loss of consciousness, as in *petit mal.* It is, perhaps, however, not so much a curative as an alleviative remedy, and the fits are apt to return when its administration is discontinued.

It is useful in relieving **sickness**, especially in pregnancy. In sea-sickness it is perhaps more useful than any other remedy. It should be taken in thirty-grain doses twice or thrice a day, for a day or two before the voyage begins, and should be kept up while it continues. In severe cases it may be necessary to push the bromide so far as to keep up a state of more or less somnolency and stupidity during the whole voyage.

From its power of lessening the sexual passion it is used as an **anaphrodisiac** in priapism and nymphomania.

It is also useful in menorrhagia, especially when this occurs in young women, according to Ringer, while Garrod says it is more useful in old women.

It is useful in neuralgia occurring in debilitated subjects, and sometimes accompanied by flushed face with cold hands and feet. It has been used in diabetes.

Sodii Bromidum, B. and U.S.P. BROMIDE OF SODIUM. (NaBr; 102·8.)

CHARACTERS.—Small, colourless, or white monoclinic crystals, or a crystalline powder permanent in dry air, odourless, having a saline, slightly bitter taste, and a neutral or faintly alkaline reaction.

PREPARATION.—*Vide* p. 618.

SOLUBILITY.—Soluble in 1·2 parts of water and in 13 parts of alcohol at 15° C. (59° F.)

REACTIONS.—It gives the reactions of sodium (p. 617), and if disulphide of carbon be poured into a solution of the salt, then chlorine water added drop by drop, and the whole agitated, the disulphide will acquire a yellow or yellowish-brown colour (bromide) without a violet tint (absence of iodide).

DOSE.—10 to 60 grains.

ACTION.—Its actions are the same as those of bromide of potassium, but it is said to be less irritating to the stomach, and less apt to cause depression when used for a length of time.

Ammonii Bromidum, B. and U.S.P. BROMIDE OF AMMONIUM. (NH_4Br; 97·8.)

CHARACTERS.—In colourless crystals which become slightly yellow by exposure to the air, and have a pungent saline taste.

PREPARATION.—*Vide* p. 635.

REACTIONS.—Its solution gives the reactions of ammonia (p. 634), and a bromide (p. 594).

DOSE.—2 to 20 grains.

USES.—The bromide of ammonium has been employed for the same purposes as the bromide of potassium. It may be used in cases where the bromide of potassium appears to cause depression, either instead of the potassium salt, or mixed with it, and the mixture of bromide of potassium with bromide of ammonium has been supposed to have a better action than either salt alone. The best proportion is said to be that of 1 part of bromide of potassium, 1 of bromide of sodium, and ½ of bromide of ammonium.[1]

U.S.P. Lithii Bromidum. BROMIDE OF LITHIUM. ($LiBr$; 86·8.)

CHARACTERS.—A white granular salt, very deliquescent, odourless, having a very sharp, somewhat bitter taste, and a neutral reaction.

PREPARATION.—*Vide* p. 631.

SOLUBILITY.—Very soluble in water and in alcohol.

REACTIONS.—Those of lithium (p. 630) and of a bromide (p. 594).

DOSE.—15–30 grs.

ACTION.—The same as that of bromide of potassium. It is said by some to have a stronger hypnotic action than the other bromides, but by others to be less effective than the potassium salt.

USES.—The same as those of potassium bromide. It may be preferable to the potassium salt in the irritability of gouty subjects.

U.S.P. Calcii Bromidum. BROMIDE OF CALCIUM. ($CaBr_2$; 199·6.)

CHARACTERS.—A white granular salt, very deliquescent, odourless, having a pungent saline and bitter taste, and a neutral reaction.

PREPARATION.—By adding milk of lime to a boiling solution of ammonium bromide.

REACTIONS.—An aqueous solution of the salt yields the reactions of calcium (p. 646) and a bromide.

USES.—15 to 30 grains (1 to 2 gm.).

DOSE.—The same as those of potassium bromide (p. 553). It is said not to depress like the potassium bromide.

U.S.P. Zinci Bromidum.—*Vide* p. 672.

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[1] Erlenmeyer, *Centbl. f. Nervenhk.* 1884. No. 4.

IODUM. I; 127 or 126·6, U.S.P.

Iodine.—A non-metallic element obtained from the ashes of sea-weeds and from mineral iodides and iodates.

CHARACTERS.—Heavy, bluish-black, rhombic plates of a peculiar odour and metallic lustre, which, when heated, yield a beautiful violet-coloured vapour.

PREPARATION.—*Vide* p. 548.

SOLUBILITY.—It is very sparingly soluble in water, but freely dissolved by alcohol, by ether, and by a solution of iodide of potassium.

REACTION.—The aqueous solution strikes a deep blue colour with starch.

IMPURITIES.—Moisture, metallic impurities fraudulently added, cyanide of iodine (the nitrogen in this is yielded by marine animals amongst the sea-weed), chloride of iodine, chlorine and bromine.

TESTS.—It should not adhere to the sides of the bottle, and its solution in chloroform should be clear and limpid (absence of moisture). It sublimes as a purple vapour without leaving any residue (absence of fixed impurities), and the portion that first comes over does not include any slender colourless prisms emitting a pungent odour (absence of cyanide of iodine); 12·7 grains dissolved in an ounce of water containing fifteen grains of iodide of potassium require for complete discoloration 1,000 grain-measures of the volumetric solution of hyposulphite of sodium.

PREPARATIONS, B.P.

Arsenii Iodidum.
Emplastrum Plumbi Iodidi.
Hydrargyri Iodidum Rubrum.
Iodoformum.
***Linimentum Iodi** (p. 516).
Linimentum Potassii Iodidi cum Sapone (p. 516).
***Liquor Iodi,** aqueous solution (1 in 20).
Pilula Ferri Iodidi (p. 522).
Plumbi Iodidum.
Potassii Iodidum.
Sodii Iodidum.
Sulphuris Iodidum.
Syrupus Ferri Iodidi.
***Tinctura Iodi,** alcoholic solution (1 in 40).
Unguentum Hydrargyri Iodidi Rubri.
* ,, **Iodi** (1 in 31).
,, Plumbi Iodidi.
,, Potassii Iodidi.
,, Sulphuris Iodidi.
***Vapor Iodi** (Tincture of Iodine, 1 fl. dr. mixed with 1 fl. oz. of water, gently warmed, and the vapour inhaled).

U.S.P.

Ammonii Iodidum.
Argenti Iodidum.
Arsenici Iodidum.
*Liquor Iodi Compositus (5 in 100).
Plumbi Iodidum.
Potassii Iodidum.
Sodii Iodidum.
Sulphuris Iodidum.
Tinctura Iodi (8 in 100).
*Unguentum Iodi (4 in 100).
,, Plumbi Iodidi.
,, Potassii Iodi.
Zinci Iodidum.

The preparations marked with * in the preceding list contain iodine in a free state dissolved by the aid of iodide of potassium (p. 556). Tinctura Iodi U.S.P. contains free iodine dissolved in alcohol. The others contain it in a state of combination.

U.S.P. Liquor Iodi Compositus. Iodine 5, iodide of potassium 10, distilled water 85. This solution differs from Liquor Iodi P.B., only in containing 10 per cent. of iodide of potassium, while the B.P. preparation contains 7½ per cent.

Sulphuris Iodidum. B.P. and U.S.P. IODIDE OF SULPHUR.

CHARACTERS.—Greyish-black, crystalline lumps. It smells like iodine and stains the skin. When boiled with water it is decomposed, iodine passing off and sulphur remaining.

PREPARATION.—By fusing iodine and sublimed sulphur together.

OFFICINAL PREPARATION, B.P.

Unguentum Sulphuris Iodidi.—Ointment of iodide of sulphur (30 grains to an ounce of prepared lard).

Iodine is rendered much more soluble either in water or spirit by the addition of iodide of potassium, hence this substance is used in the liniment, liquor, tincture, and ointment of the B.P., and in the compound solution and ointment of the U.S.P. It is not contained in the tincture of the U.S.P., which is a simple solution of iodine in alcohol.

DOSE.—The only preparations of iodine used for internal administration are the tincture B.P. and U.S.P., the liquor B.P. and compound solution U.S.P., of all of which the dose is 5 to 20 minims.

PHYSIOLOGICAL ACTION.—Like chlorine and bromine, iodine is a powerful antiseptic and oxidising agent. When applied to the unbroken **skin**, iodine stains it of a dark yellowish-brown colour, causes slight warmth, and afterwards a little itching. In stronger solutions it will cause a painful burning sensation, and desquamation of the epidermis. In still stronger solution it may produce vesication. When taken internally, in small doses, it acts as an irritant to the **intestinal canal**, causing catarrh of the mucous membrane. When absorbed into the blood it somewhat increases the rapidity of the **pulse**. It has little action upon blood-pressure. Its influence upon the **temperature** is very slight, but it seems rather to raise it. Iodine appears to have a tendency to cause **absorption** of enlarged glands and thickenings caused by chronic inflammation. It seems to combine with such metals as lead and mercury, which have become deposited in the tissues in cases of chronic poisoning, forming with these soluble iodides, which are eliminated in the same way as iodine itself. It is **eliminated** by the urine, nasal mucous membrane, saliva, intestinal mucus and milk, in all of which it may be readily detected. It appears to be eliminated even more readily by the saliva than by the urine (p. 358), and on this account it may remain a considerable time in the body. During the process of elimination it may irritate those parts where it is set free from its compounds, as the nose or skin. Even in small doses it may cause symptoms of **iodism.** These consist in irritation, either of the nose or intestinal tract; the most prominent are great running at the nose, lacrimation, and sometimes frontal headache. Similar symptoms are produced by exposure to the fumes of iodine for a length of time. The nasal symptoms may be accompanied or replaced by symptoms of gastric irritation, loss of appetite, slight nausea, and tendency to looseness of the bowels. The **symptoms of poisoning**, such as have occurred from the injection of large quantities of iodine solution into an ovarian cyst, were, first, collapse, followed after a little while by an appearance of fever,

with rapid pulse and flushed face, but without any rise of temperature. This condition passed off in several days, but during apparent convalescence the patient suddenly died. Small doses of iodine, by improving the health of patients, may increase the menstrual flow, and may act as aphrodisiacs. Larger doses generally have a very marked **anaphrodisiac** action, and it has been stated that long-continued use has produced atrophy of the mammæ, ovaries, and testes. It has been stated that very large doses affect the **nervous system**, causing delirium, and twitching or paralysis of the muscles (p. 549).

USES.—Iodine applied to the epidermis acts as a **parasiticide**, and may be used in cases of tinea to destroy the fungus, either alone or combined with tar in the proportion of two drachms of iodine to one ounce of light oil of wood tar. Its solution, painted on the surface, is useful in removing muscular pains, and in causing absorption of thickening around joints, or of enlarged strumous glands. When painted on the surface it sometimes causes absorption of the enlarged thyroid gland in goître, and, when outward application is insufficient, success is sometimes obtained by injecting from ten to thirty minims of tincture of iodine into the substance of the tumour by means of a hypodermic syringe, care being taken to avoid injection into a vein. Its solution, painted on the surface, is also useful in causing absorption of fluid from serous cavities, as in pleurisy. Sometimes, after the fluid has been evacuated from a serous sac, such as the pleura, or the tunica vaginalis in hydrocele, or from ovarian cysts, a dilute tincture of iodine is injected into the sac to prevent the fluid from again accumulating.

In removing slight consolidation of the lung, remaining after pneumonia or pleurisy, or in cases of commencing phthisis, the external application of liniment of iodine is very useful. It should be painted on the surface, every second or third day, so as always to keep one part a little tender. By mixing the liniment with the tincture in varying proportions any degree of strength can be obtained. Cases of ozæna are sometimes much benefited by washing out the nose with a solution of common salt to which a few drops of tincture of iodine have been added. The vapour of iodine is employed in chronic bronchitis and phthisis.

On account of its irritating action on the intestinal mucous membrane, iodine is rarely given internally, its place being supplied by iodide of potassium, but some consider that iodine is sometimes more effectual, and it has been given in scrofula, skin diseases, and glanders.

The liquor iodi B.P., or compound solution of iodine U.S.P., is useful in arresting vomiting when administered internally in doses of 3 to 5 minims.

Potassi Iodidum, B. and U.S.P. IODIDE OF POTASSIUM. (KI; 165·6.)

CHARACTERS.—In colourless, generally opaque, cubic crystals.

PREPARATION.—By mixing iodine and solution of potassa, when iodide and iodate of potassium are formed, $6KHO + 6I = KIO_3 + 5KI + 3H_2O$. The iodate is then reduced to iodide by roasting with charcoal, $5KI + KIO_3 + 3C = 6KI + 3CO$.

SOLUBILITY.—It is readily soluble in water, and in a less degree in spirit.

REACTIONS.—It commonly has a feeble alkaline reaction; its solution gives the reactions of potassium (p. 603) and an iodide (p. 594).

IMPURITIES.—Iodate from imperfect reduction, chlorides, sulphates, carbonates. Iodate is the most important impurity, since the dilute acid of the gastric juice will form hydriodic acid from the iodide, and this will liberate free iodine from the iodate in the stomach, and thus give rise to such gastric irritation that the iodide cannot be borne in doses where pure iodide would be readily tolerated.

TESTS.—The addition of tartaric acid, B.P., or dilute sulphuric acid, U.S.P., and mucilage of starch, B.P., or gelatinised starch, U.S.P., to its watery solution does not develop a blue colour (absence of iodate). If iodate be present the acid liberates hydriodic acid, and this re-acting on the iodate forms free iodine, $6HI + KIO_3 = 3H_2O + KI + I_6$. Solution of nitrate of silver added in excess forms a yellowish-white precipitate, which, when agitated with ammonia, yields on standing a clear liquid in which excess of nitric acid causes no turbidity, B.P. (absence of chloride). Iodide of silver is insoluble in ammonia, but chloride is readily soluble, so the chlorides, if present, would be taken up by the ammonia and re-precipitated on the addition of acid. Its aqueous solution is only faintly precipitated by the addition of saccharated solution of lime.

DOSE.—2 to 10 grains.

PREPARATIONS CONTAINING IODIDE OF POTASSIUM.

B.P.	STRENGTH.
Linimentum Iodi (p. 516)	22 grs. in 1 fl. oz. nearly.
„ **Potassii Iodidi cum Sapone** (p. 516)	$54\frac{1}{2}$ grs. in 1 fl. oz. nearly.
Liquor Iodi	33 grs. in 1 fl. oz.
Tinctura Iodi (Dose, 1–5 min.)	11 grs. in 1 fl oz. nearly.
Unguentum Iodi	16 grs. in 1 oz. nearly.
„ **Potassii Iodidi**	1 part in $8\frac{3}{4}$, nearly.

U.S.P.	DOSE.
Unguentum Potassii Iodidi	
Liquor Iodi Compositus	2–6 min. (0·10–0·40 c.c.).

Unguentum Potassii Iodidi, B. and U.S.P. OINTMENT OF IODIDE OF POTASSIUM.—Iodide of potassium 64 grains, carbonate of potassium 4 grains, distilled water 1 fluid drachm, prepared lard 1 ounce. Dissolve the iodide of potassium and carbonate of potassium in the water, and mix thoroughly with the lard. B.P.

Iodide of potassium 12, hyposulphite of sodium 1, boiling water 6, benzoated lard, 81. U.S.P.

The ointment is apt to become discoloured by the liberation of free iodine when iodide of potassium and lard only are used. The carbonate of potassium, B.P., is added in order that it may combine with any iodine set free, and the hyposulphite, U.S.P., is also used to prevent this discoloration.

ACTION.—The action of iodide of potassium appears to depend partly on the iodine and partly on the potassium it contains. It differs from that of free iodine (p. 558) in being much less irritant. On this account it is of little use as a local stimulant,

but it can be given in much larger doses. It has been supposed that iodine is set free from iodides in the stomach; but probably this is not the case, at least to any great extent, unless the iodides are contaminated with iodates. Iodide of potassium and other alkaline iodides are readily **absorbed.** It is conveyed by the blood to the various tissues of the body. It has been supposed by Binz to be partially **decomposed** by some of them, with the evolution of free iodine both in the blood and in the tissues, and he attributes its most important actions to this decomposition. The iodine set free from the iodide is taken up by **albuminous substances**, and the entrance of the iodine molecule into their composition causes them to undergo more rapid metamorphosis. Gummatous deposits appear to be especially affected in this way.

Lead and **mercury** also appear to be set free by it, from their combinations with the tissues, and entering once more into the circulation are eliminated. Iodides are **eliminated** very rapidly by the kidneys, salivary glands, probably by all mucous membranes, and by the skin. During the process of elimination iodine is occasionally set free and causes local irritation. This is especially marked in the mucous membrane of the **nose**, and in the skin, but it may occur also in the conjunctivæ, bronchi, and stomach. The irritation of the nasal mucous membrane thus produced gives rise to the symptoms generally known as **iodism.** They are exactly the same as those produced by prolonged exposure to the fumes of iodine. They consist of running at the nose, and frontal headache, which probably depends upon swelling of the mucous membrane lining the frontal sinuses. There is also frequently running of the **eyes.** Not unfrequently the **bronchial** mucous membrane becoming congested there is cough and pain in the chest. These symptoms are most readily produced by small doses of 2–5 grains, and they may usually be arrested either by discontinuing the medicine or increasing the dose. When the dose is raised to 10 grains the symptoms usually disappear, and I have only seen one case in which they persisted after the dose had been raised to 30 grains. In some persons the congestion is not confined to the nose, but extends to the back of the throat and to the **larynx**, so that serious symptoms of suffocation may follow the laryngeal congestion produced in them by iodide. As the iodine is eliminated in the tears, severe conjunctivitis may follow the application of calomel to the eyes of persons who are taking iodide at the same time. Affections of the **skin** usually occur with large doses of iodide. The most common form of eruption is acne, but tubercular eruptions are also met with. They appear to be caused by decomposition of the iodide with elimination of free iodine in the sweat and sebaceous matter. They are said to be lessened by the simultaneous use of arsenic, and to be prevented by perfect cleanliness

and daily baths. Occasionally the iodide causes **gastric** irritation with diminished appetite. It is readily excreted by the **salivary** glands, and may give rise to salivation (p. 358). It sometimes gives rise not only to congestion of the bronchial mucous membrane and cough, but to hæmoptysis, exudation into the pleural cavity, and even pneumonic consolidation.

In some persons it greatly depresses the **genital** functions.

During its excretion by the **kidneys** it acts as a diuretic, though not a very powerful one.

Uses.—Although iodide of potassium is probably absorbed in very small quantity by the unbroken skin, even when mixed with oil or fat, yet the iodide of potassium and soap liniment, especially when mixed with its own bulk of opium liniment, sometimes gives considerable relief when applied to inflamed and rheumatic joints by means of flannel or lint. When used with lanolin, it is said to be more readily absorbed and to give still greater relief in chronic joint disease. Iodide of potassium is chiefly used, however, internally in syphilis, rheumatism, scrofula, and chronic poisoning by lead or mercury. In the primary and secondary stages of syphilis, mercury is generally used either alone or in combination with iodine. In the tertiary stage, iodide of potassium is more generally given alone, although it is said by some to have but little effect unless mercury has been administered at some previous time. If this opinion be correct, the beneficial action of iodide of potassium may be due, in part at least, to its again liberating part of the mercury which has been in a state of more or less dormant combination with some of the tissues. The powerful action of iodide of potassium in removing syphilitic deposits is readily seen when these deposits are superficial, as nodes on the shin or on the sternum, or when they can be readily seen, like deposits in the larynx. Sometimes such deposits are unaffected by small doses, such as five grains of iodide, but disappear rapidly when the dose is increased to ten grains or more. From its beneficial action on visible deposits we may infer that it has a similar action on those which are deeply situated, and indeed sometimes we may observe enlargement and induration of the liver, probably dependent on a syphilitic condition, rapidly disappear under the use of the iodide. In chronic rheumatism, especially when the pain is worse at night, it is sometimes useful.

It apparently increases the activity of the lymphatic system, and is used in enlargement of glands connected with this system, e.g. enlarged thyroid, enlarged spleen, and the enlarged lymphatic glands which occur in scrofula, as well as in scrofulous conditions generally.

It is given wherever absorption is deficient and organs become hypertrophied, e.g. the breasts, testicles, prostate, uterus, ovaries,

&c. In cancer and tubercle it is of little benefit; it is sometimes given, and possibly with benefit, in order to aid the absorption of pneumonic consolidation.

In bronchitis with much congestion and deficient secretion it is a useful expectorant, rendering the mucus more abundant and less tenacious, so that it is more readily expectorated.

As syphilitic skin-diseases often disappear under its use, it has been applied to other skin-diseases not dependent on syphilis, such as psoriasis, lepra, herpes, impetigo, lichen, prurigo, sycosis, acne, lupus, &c., especially in scrofulous patients.

In frogs it destroys sensibility and voluntary motion by acting on the spinal cord. It is useful in large doses to diminish the pain in cases of aneurism, and is also used in neuralgia, paralysis, convulsions, &c.

The relief which it affords to the pain of aneurism is very marked, but it must be given in large doses, e.g. thirty grains. The benefit which it affords may be partly due to weakening of the circulation, partly to diminished sensibility by the action of the drug on the nervous system, and partly to beneficial alterations in the morbid condition of the walls of the affected vessels, which are often syphilitic in character.

It is exceedingly useful, as already mentioned, in chronic metallic poisoning, e.g. by mercury or lead.

It is used in dropsies as a diuretic, and is also employed as an emmenagogue.

Sodii Iodidum, B. and U.S.P. Iodide of Sodium. NaI; 149·6.

Characters.—Minute, colourless, or white monoclinic crystals, or a crystalline powder, deliquescent on exposure to air, odourless, having a saline and slightly bitter taste and a neutral or faintly alkaline reaction.

Solubility.—Soluble in 0·6 part of water and in 1·8 parts of alcohol at 15° C. (59° F.).

Reaction.—If disulphide of carbon be poured into a solution of the salt, then chlorine water added drop by drop, and the whole agitated, the disulphide of carbon will acquire a violet colour.

Dose.—3 to 30 grains.

Uses.—It is employed in place of iodide of potassium. Its physiological actions are almost exactly the same, but it appears to be less depressing and to irritate the stomach less. It may thus be given in larger doses.

U.S.P. Ammonii Iodidum. Iodide of Ammonium. NH_4I; 144·6.

Characters.—A white granular salt, or minute crystalline cubes, very deliquescent and soon becoming yellow or yellowish-brown on exposure to air; odourless when white, but emitting a

slight odour of iodine when coloured, having a sharp saline taste and a neutral reaction.

USES.—A solution of $\frac{1}{2}$-drm. in an ounce of glycerine has been used as an application to enlarged tonsils. An ointment containing 20 to 60 grs. of the iodide to 1 oz. of lard has been used in cases of lepra and psoriasis. It is chiefly used internally for syphilis, scrofula, and glandular enlargements, either instead of or along with iodide of potassium. A mixture of the two iodides has been thought by some to be more efficacious than either used singly, and the iodide of ammonium prevents the depressing action often exerted by the iodide of potassium alone.

U.S.P. Zinci Iodidum.—*Vide* p. 673.

U.S.P. Argenti Iodidum.—*Vide* p. 680.

Hydrargyri Iodidum Rubrum, B. and U.S.P. — *Vide* p. 696.

U.S.P. Hydrargyri Iodidum Viride.—*Vide* p. 696.

Plumbi Iodidum, B. and U.S.P.—*Vide* p. 705.

The action of the iodides of zinc, silver, mercury, and lead is modified to such an extent by the special action of the metal, that the compounds are better considered under the headings of their respective metals (*q.v.*) than side by side with the compounds with the alkalis.

CHAPTER XXIII.

ACIDS.

General Characters.—It is somewhat difficult to get a correct definition of an acid. Most of them have a sour taste and redden blue litmus: they combine with alkalis and destroy the power which these have of turning red litmus-paper blue.

They may be regarded as compounds of hydrogen with certain radicals, hydrogen being readily displaced by other bases. Some acids, as boric and carbolic, have no sour taste. Carbolic acid does not redden litmus-paper, but it is in reality an alcohol, although in chemical combinations it behaves like an acid.

General Preparation of Acids.—Most acids are prepared by liberating them from their alkaline salts by means of sulphuric acid. When they are volatile they are separated by distillation, and when non-volatile by crystallisation.

Sulphuric acid, which is of such importance in the preparation of other acids, is itself prepared by oxidising the fumes of sulphur by means of nitric acid. Sulphur is burnt, and the sulphurous oxide thus produced is conducted along with the vapour of nitric acid into a large leaden chamber, where it is mixed with steam. Sulphurous oxide is oxidised by the nitric acid and sulphuric oxide is formed, which uniting with the watery vapour forms sulphuric acid. The nitric acid is deoxidised in this process into nitric oxide; this unites with the oxygen of the air to form nitric peroxide, and this again supplies fresh oxygen to the sulphurous acid, $NO_2 + SO_2 + H_2O = NO + H_2SO_4$. In this way a small quantity of nitric acid is sufficient to oxidise a large quantity of sulphuric acid; reduction and reoxidation going on alternately in the nitrous fumes. The sulphuric acid formed in the leaden chamber is drawn off and evaporated to the proper strength.

The acids which are prepared by liberation from their salts by sulphuric acid are given in the following tables:—

Volatile Acid	Prepared from	By addition of Sulphuric Acid and
Carbonic Acid . .	Any carbonate, generally Carbonate of Calcium	Conducting into water or alkaline solution, according to the purpose required.
Hydrochloric Acid, B. and U.S.P.	Sodium chloride .	Distilling into water, which dissolves the acid.
Nitric Acid, B. and U.S.P.	Sodium Nitrate, or Potassium Nitrate	Distilling.
Acetic Acid, B. and U.S.P.	Crystallised Sodium Acetate	Ditto.
Glacial Acetic Acid, B. and U.S.P.	Dried Sodium Acetate	Ditto.
Dilute Hydrocyanic Acid, B. and U.S.P.	Potassium Ferrocyanide	Distilling into water.

Sodium chloride and sodium nitrate are found native: the sodium acetate is prepared from gas liquor by saturating with sodium carbonate.

In preparing hydrocyanic acid the cyanide is not employed, but the ferrocyanide which is prepared by heating together animal refuse and iron filings and potassium carbonate.

Non-Volatile Acid	Prepared from	By addition of Sulphuric Acid and
Chromic Acid . .	Potassium Bichromate	Collection of crystals, draining, and drying.
Tartaric Acid, B. and U.S.P.	Tartrate of Calcium, made from acid tartrate of potassium	Subsequent decantation from calcium sulphate, evaporation and crystallisation.
Citric Acid, B. and U.S.P.	Citrate of Calcium, made from lemon-juice	Subsequent decantation, &c., as for tartaric acid.
Lactic Acid, B. and U.S.P.	Lactate of Calcium, obtained by peculiar fermentation of sugar	Decantation and evaporation.
Boric Acid, B. and U.S.P.	Sodium borate . . .	Precipitation; the boric acid, sparingly soluble in water, falls as a precipitate, and the sodium sulphate is removed by decantation or filtration.

If sulphuric acid were added to citrate or tartrate of potassium or sodium, it would be difficult to separate the acid from the sulphate. To avoid this, the citrates and tartrates of calcium are first prepared, and to these sulphuric acid is added. There results an insoluble calcium sulphate which falls as a precipitate, and the solution of citric or tartaric acid is readily separated by decantation or filtration, and evaporated to crystallisation.

Citrate of calcium is prepared by adding chalk to boiling lemon-juice, and washing the colouring matter from the precipitate by

hot water. Hot is employed in preference to cold water because citrate of calcium is less soluble in it. Tartrate of calcium is prepared from the crude acid tartrate of potassium or argol, which is deposited from wine during the process of fermentation. Chalk is first added to a solution of it, whereby a neutral tartrate is formed, $2(KHC_4H_4O_6) + CaCO_3 = CaC_4H_4O_6 + K_2C_4H_4O_6 + CO_2 + H_2O$. This is then decomposed by the addition of calcium chloride or sulphate, $K_2C_4H_4O_6 + CaCl_2 = CaC_4H_4O_6 + 2KCl$.

Exceptions to the rule that acids are prepared from salts by the addition of sulphuric acid :—

Acid	Prepared by
Sulphuric Acid	Combustion of sulphur and the oxidation and hydration of the resulting sulphurous acid gas by means of nitrous and aqueous vapours.
Phosphoric Acid	Oxidising phosphorus by heating it with diluted nitric acid until nitrous fumes have ceased to form, and then diluting it to the proper strength.
Oxalic Acid	Oxidising sugar by heating with nitric acid.
Sulphurous Acid	Deoxodising sulphuric acid by means of charcoal and passing the fumes into water.
Hydrobromic Acid	By passing sulphuretted hydrogen into bromine and water $2Br_2 + 2H_2S = 4HBr + S_2$.
Arsenious Acid	Roasting arsenical ores, collecting the acid which sublimes, and purifying it by resublimation.
Benzoic Acid	Heating gum benzoin when the acid sublimes.
Carbolic Acid	Fractional distillation of coal-tar oil and subsequent purification.
Oleic Acid	Decomposing lead oleate by hydrochloric acid or by decomposing fats by superheated steam and separation from solid fats by pressure.
Salicylic Acid	By passing carbonic acid gas over sodium carbolate which is made by evaporating a mixture of caustic soda and carbolic acid to dryness.
Tannic Acid	Dissolving out from the fresh nut-galls in which it is contained by ether and water.
Gallic Acid	Dissolving it out from fermented nut-galls by hot water.

Hydrobromic acid, although volatile, is not unfrequently prepared without distillation. McLean Hamilton and Milner Fothergill's plan is to dissolve $84\frac{1}{4}$ grs. of potassium bromide in a fluid ounce of water, and add 99 grs. of tartaric acid to it. After standing at a low temperature for twelve hours, acid tartrate of potassium crystallises out, and leaves a solution containing about 10 per cent. of real hydrobromic acid.

General Action of Acids.—They have an affinity for electro-positive or basic substances, and combine with them when they come in contact. Stronger acids drive out weaker ones from their combination with bases, setting them free; but are themselves sometimes driven out by weaker ones if these form an insoluble combination.

When they come in contact with the tissues they produce changes in a twofold manner; (1) by forming new compounds

(2) by destroying others previously existing. The different acids possess different affinities, and the actions they exert vary with the acid and with the degree of its concentration, weak acids having their affinities easily satisfied. All the **tissues** of the body are alkaline, and the first effect of acids will be to neutralise the alkali, and if albumin be dissolved in it to precipitate it. If sufficient acid be present, they all, with the exception of nitric acid, again redissolve it. Acids unite with **albumin** in different proportions, forming acid-albumin. When mixed with **blood** they not only precipitate albuminous substances, but decompose hæmoglobin, forming a substance which holds oxygen with more tenacity than hæmoglobin. They coagulate myosin and produce instantaneous rigidity in **muscles.** Sulphuric and phosphoric acids have, besides their chemical affinities, a strong attraction for water, and completely decompose the tissues to which they are applied, so that they are most powerful **escharotics.** Nitric acid does not readily redissolve the albumin precipitated by it, and thus forms a barrier to its own action, so that it does not penetrate so deeply as sulphuric acid.

Round the tissue killed by acids inflammation ensues, and an eschar is separated. When their action is less intense they cause inflammation of the surface of the dermis, and produce **vesication.** Still less concentrated, they precipitate albumin from its solutions in the tissues, act as irritants, and cause contraction of the blood-vessels. This effect is removed by the alkalinity of the blood, and the irritation may be only sufficient to cause a temporary congestion subsequent to the contraction. Then the acids act only as **rubefacients.** As such they are used in the form of baths.

In the **mouth** they cause a peculiar taste, and a feeling of roughness in the teeth. They cause an increased flow of saliva from the parotid, and of the thin saliva which the submaxillary secretes when the chorda tympani is irritated, but have no effect on the sympathetic saliva. They are therefore given to allay thirst in fever, the increased secretion of saliva which they provoke keeping the fauces moist (p. 357).

Acids stimulate the secretion of the alkaline saliva and intestinal juice, and excite the expulsion of bile from the gall-bladder. They are supposed generally to stimulate those glands whose secretions are alkaline. On the other hand alkalis stimulate the secretion of gastric juice, which is acid ; and they are supposed to stimulate in general those glands whose secretion is acid. Professor Ringer supposes that the converse is also the case, and that acids and alkalis severally hinder the secretions of a like character. This supposition may be correct, and no doubt when an acid is present—e.g. in the stomach—it will neutralise any alkali which may be taken, and either retard its stimulant action on the gland or prevent it altogether, according

to the relative quantities of acid present and of alkali employed. The presence of much alkali will also hinder the action of an acid stimulus in the same manner, but whether acids and alkalis have any further effect in hindering secretion than that just mentioned is uncertain.

Acids are partly neutralised by the saliva, and partly act as astringents on the mouth and fauces. They are thus used in congestion of the throat. As they corrode the teeth, they are generally given through a glass tube or quill, and the teeth should be rubbed with chalk afterwards.

Digestion in the **stomach** is accomplished by the action of pepsin along with dilute hydrochloric acid (·2 per cent. in man). This ferment only acts in presence of free acid; but the amount of acid necessary is different in different animals, being greatest in the carnivora (·3 per cent. HCl in the dog) and least in the herbivora. Pepsin seems able to go on dissolving fibrin almost without a limit, but fresh acid must always be added. If the secretion is deficient, digestion goes on slowly and fermentation of the food takes place, causing the formation of other acids and liberation of gases.

The secretion of gastric juice may be stimulated by alkalis given just before meals; but if the stomach is so much out of order as not to respond to the stimulus, hydrochloric or phosphoric acid may be given after meals, alone, or with pepsin. In febrile conditions there is a deficiency of free acid in the stomach, although pepsin is present in plenty. In chronic gastric catarrh, especially when accompanied by dilatation, the free acid is greatly diminished, and in carcinoma of the stomach it would seem to be wanting in the great majority of cases. In such conditions, therefore, the administration of diluted hydrochloric acid is indicated.

For acid eructations and heartburn depending on excessive acidity of the gastric juice, acids should be given before meals (Ringer).

Some persons are troubled by eructations of sulphuretted hydrogen with a taste of rotten eggs. These persons have generally oxalic acid in the urine, and frequently suffer from depression of spirits. Such patients are benefited by acids, especially nitro-hydrochloric acid. Persons who suffer from dyspepsia and depression of spirits with oxaluria are also benefited by mineral acids, even when no sulphuretted hydrogen is present in the intestines.

When the use of acids is long continued they lessen the secretion of gastric juice, and produce a catarrhal condition of the mucous membrane of the stomach. They should therefore not be given for more than a week or two at a time. They should then be left off for a short time, or alternated with alkalis. Constant use of acid wines has a similar tendency to produce

catarrh. Vinegar is sometimes drunk in order to lessen obesity or even plumpness. It has this effect by inducing gastro-intestinal catarrh, but sometimes the derangement of the digestion occasioned by it has been so great as to cause death.

Acids stimulate the expulsion of bile from the gall-bladder, and the secretion of intestinal juice. As they will be rapidly neutralised by the bile and pancreatic juice, and absorbed in the duodenum, they can hardly reach the lower and middle parts of the alimentary canal as acids. Their action in relieving diarrhœa is difficult to explain.

When absorbed from the intestine they must pass through the liver before they can reach the general circulation (p. 399 *et seq.*). It is probable that during their passage through the portal system they alter the processes of tissue-change which go on in the liver, and check the formation of urea. The reason for this supposition is that acids are excreted in the urine chiefly in the form of ammoniacal salts. In the normal condition ammonia is readily converted into urea in the organism, and when given internally it appears in the urine in the form of urea, and not of ammoniacal salts. The appearance of these salts in the urine after the administration of acids shows that the normal process of conversion into urea has been diminished. Possibly it is to such alterations in the tissue-change in the liver that the so-called tonic action of acids is due (p. 410), as well as the marked benefit obtained in hepatic disorders from the administration of nitric and nitro-hydrochloric acids. Although acids appear in the urine in combination with ammonia and other bases, yet their free administration increases the acidity of the urine. They are therefore used to prevent the deposits of phosphatic calculi which are apt to occur in alkaline urine.

Poisoning by Acids.—The symptoms of poisoning by acids, and the antidotes to be employed, have already been described (pp. 395, 397, and 486). In cases of acute poisoning where death has not occurred too quickly, much albumen, hæmatin, and indican have appeared in the urine, and fatty degeneration of the liver, muscles, and kidneys has been found. In the kidneys the cloudy swelling and fatty degeneration of the cells were accompanied by evidences of inflammation in the connective tissue also, as it exhibited proliferation of nuclei, especially along the course of the vessels.

Acidum Sulphuricum, B. and U.S.P. Sulphuric Acid.—It contains 96·8 per cent. of H_2SO_4 (98) and corresponds to 79 per cent. of anhydrous sulphuric acid, SO_3 (80).

Properties.—A colourless, oily-looking, heavy liquid. Sp. gr. 1·843; no smell, but intensely acid taste. It blackens and corrodes most organic substances. It has a great affinity for water, and when mixed with it evolves much heat. When diluted it

gives a copious white precipitate of barium sulphate ($BaSO_4$) with chloride of barium, insoluble in nitric or in hydrochloric acid.

PREPARATION.—*Vide* p. 565.

IMPURITIES.—Lead derived from the leaden chambers in which it is prepared; nitric acid from the nitrous fumes; arsenic from impure sulphur being used and the arsenious fumes passing over with the sulphurous acid; and water from imperfect concentration or fraudulent addition.

TESTS.—Not unfrequently it contains so much lead in the form of sulphate that when diluted with water it deposits a white precipitate, the sulphate being soluble in the strong but not in the weak acid. It should not do this, and when evaporated in a platinum dish it should leave little or no residue (no lead, arsenic, or saline impurities). When a solution of sulphate of iron is carefully poured over its surface there is no purple colour developed where the two liquids unite (no nitric acid). Diluted with six times its volume of distilled water it gives no precipitate with sulphuretted hydrogen (no arsenic or lead). The absence of water is ascertained by the sp. gr. not being below 1·840, and by the volumetric estimation of its neutralising power with solution of soda.

OFFICINAL PREPARATIONS.

B.P.	U.S.P.
Acidum Sulphuricum Aromaticum.	Acidum Sulphuricum Aromaticum.
" " Dilutum.	" " Dilutum.
Infusum Rosæ Acidum.	

Acidum Sulphuricum Aromaticum, B. and U.S.P. AROMATIC SULPHURIC ACID. Is sulphuric acid diluted with alcohol and flavoured with cinnamon and ginger. About 1 in 13 B.P., and 1 in 10 U.S.P. by measure.

Infusum Cinchonæ Acidum contains aromatic sulphuric acid 1 part in 80.

Acidum Sulphuricum Dilutum, B. and U.S.P. DILUTE SULPHURIC ACID. Is the strong acid diluted with 11 parts B.P., 16½ parts U.S.P., of water by measure; 1 in 10 by weight U.S.P.

DOSES.—Of either aromatic or dilute sulphuric acid 5-30 min. freely diluted.

INCOMPATIBLES.—Preparations of lead.

ACTION.—It is a most powerful **caustic**, and quickly chars and destroys the parts it touches. When mixed with charcoal paste it is used as a caustic in cancer, and with lard in obstinate skin-diseases. When swallowed, as it not unfrequently is in manufacturing districts, it produces symptoms of irritant poisoning (p. 395). The antidotes are alkalis, soap, oil, whiting, milk, plaster from the wall, or magnesia.

USES.—Internally it is used, after free dilution, to quench thirst in fever, to prevent absorption of lead from the stomach in painters and colour-grinders, to check diarrhœa, especially in phthisis, to arrest hæmoptysis and other hæmorrhages, and to lessen night-sweats and mucous discharges.

Acidum Sulphurosum, B. and U.S.P. SULPHUROUS ACID.—Sulphurous acid gas (SO_2; 64) dissolved in water and constituting 9·2 per cent. of the solution.

PROPERTIES.—A colourless liquid with a strong sulphurous odour.

PREPARATION.—*Vide* p. 567, $2H_2SO_4 + C = CO_2 + 2SO_2 + 2H_2O$.

REACTIONS.—Unlike sulphuric acid, it gives no precipitate with chloride of barium, but if chlorine be added to it, it becomes converted into sulphuric acid, and then gives a precipitate, $SO_2 + 2H_2O + Cl_2 = H_2SO_4 + 2HCl$.

IMPURITIES.—Sulphuric acid, solid impurities, too little sulphurous acid.

TEST.—It should give no precipitate, or only a slight one, with chloride of barium (little or no sulphuric acid); but very few specimens answer either to this test or to the officinal volumetric test, on account of the liability of the acid to decompose. It should leave no residue on evaporation. Its strength is determined by its sp. gr. 1·04, and the volumetric test.

DOSE.—½–1 fluid drachm diluted with water.

ACTION.—It is a powerful deoxidising agent. It is extremely destructive to plant life, and so may destroy disease-germs.

USES.—Gaseous sulphurous acid is used to **disinfect** rooms. The room should be closely shut up, and a brazier with charcoal placed in it. On this sulphur is thrown, and the fumes are allowed to permeate the room for several hours. Care must be taken that the brazier is so placed that there is no danger of anything in the room catching fire. A solution mixed with glycerine may be applied in skin-diseases depending on parasitic fungi. It is very useful in cases of vomiting, especially when the vomited matters have a frothy or yeasty appearance due to the presence of sarcinæ and to the occurrence of fermentation in the stomach. Applied as spray it sometimes gives relief in laryngeal phthisis.

Acidum Hydrochloricum, B. and U.S.P. HYDROCHLORIC or MURIATIC ACID.—Hydrochloric acid gas (HCl; 36·4) dissolved in water, and forming 31·8 B.P., 31·9 U.S.P., per cent. by weight of the solution.

PROPERTIES.—A nearly colourless liquid, sp. gr. 1·16. It emits white vapours having a pungent odour, and has a strongly acid taste.

PREPARATION.—By warming chloride of sodium with sulphuric acid, washing the evolved HCl, and conducting it into cold water by which it is absorbed. Excess of sulphuric acid is employed if glass vessels are used in the preparation either of this or of nitric acid, as the bisulphate of potassium left behind is more soluble than the neutral sulphate, and thus the vessels are more easily cleaned. $NaCl + H_2SO_4 = NaHSO_4 + HCl$.

REACTION.—It gives with nitrate of silver a curdy white precipitate soluble in excess of ammonia, insoluble in nitric acid.

IMPURITIES.—Salts; sulphuric acid, with its impurities lead and arsenic; chloride of sodium or chlorine; sulphurous acid formed from sulphuric by organic substances; iron from the apparatus in which it is made commercially.

Arsenic is of importance as an impurity because hydrochloric acid is sometimes used in testing for arsenic by the formation of arseniuretted hydrogen. When testing for arsenic in cases of suspected poisoning both the acid and the zinc must be tested first, in order to ascertain their purity before the suspected substance is added.

TESTS.—When diluted with four times its volume of distilled water it gives no precipitate with solution of chloride of barium (absence of sulphuric acid), or with sulphuretted hydrogen (absence of lead or arsenic), and does not tarnish or alter the colour of bright copper foil when boiled with it

(absence of arsenic). When diluted with five volumes of water it should not liberate iodine from iodide of potassium (absence of chlorine); and when 1 c.c. is diluted to 10 c.c. with water and supersaturated with ammonia, the addition of two drops of ammonium sulphide causes no black colour (absence of iron). If a fluid drachm of it mixed with half an ounce of distilled water be put into a small flask with a few pieces of granulated zinc, and while the effervescence continues a slip of bibulous paper wetted with solution of sub-acetate of lead, B.P., or nitrate of silver, U.S.P., be suspended in the upper part of the flask above the liquid for about five minutes, the paper will not become discoloured (absence of sulphurous or arsenious acid, $SO_2 + 6H = H_2S + 2H_2O$). When evaporated it leaves no residue (no sodium chloride or other fixed impurity).

PREPARATIONS CONTAINING FREE HYDROCHLORIC ACID.

B.P.	DOSE.
Acidum Hydrochloricum Dilutum (acid 8, diluted with water up to 26½ by measure)	10–30 m.
Acidum Nitro-hydrochloricum Dilutum	10–30 m.
Liquor Antimonii Chloridi	
,, Arsenici Hydrochloricus	
,, Morphinæ Hydrochloratis	
U.S.P.	
Acidum Hydrochloricum Dilutum (acid 6, water 13 by weight; 5½ and 14 by measure)	10–30 m.
Acidum Nitro-hydrochloricum	
,, ,, ,, Dilutum	10–30 m.

ACTION AND USES.—It produces symptoms of poisoning like those of sulphuric acid. The stains which it leaves upon the mucous membrane are white. It is rarely used externally. It may be employed to quench thirst in fevers, and to lessen phosphatic deposits in the urine; it is sometimes useful in cases of sore-throat. As it is the acid of the gastric juice, it may be given after meals in cases of indigestion, where we suspect deficiency of acid (p. 568), and to aid the digestion of food, as well as to relieve thirst in febrile conditions (pp. 360 and 569).

Acidum Hydrobromicum Dilutum, B. and U.S.P. DILUTED HYDROBROMIC ACID.—A liquid composed of 10 per cent. of real or gaseous hydrobromic acid (HBr; 80·8) and 90 of water.

CHARACTERS.—A clear, colourless liquid, odourless, having a strongly acid taste and an acid reaction. Sp. gr. 1·077. By heat it is completely volatilised.

REACTIONS.—On adding chlorine or nitric acid to diluted hydrobromic acid, bromine is liberated, which is soluble in chloroform or in disulphide of carbon, imparting to these liquids a yellow colour. Test solution of nitrate of silver causes a white precipitate, insoluble in nitric acid and in water of ammonia, and sparingly soluble in stronger water of ammonia.

TESTS.—On being kept for some time, the acid should not become coloured. Test-solution of chloride of barium should not produce a turbidity or precipitate (sulphuric acid).

DOSE.—15 to 50 min. B.P. Two fluid drachms contain 12 grains of bromine, which are equal to about 18 grains of bromide

of potassium (United States Dispensatory). It may be given in syrup.

Action and Uses.—It appears to act as a **sedative** to the nervous system, diminishing reflex action and lessening tendency to spasm, in the same way as bromide of potassium, but differing from it in not producing the feeling of depression frequently caused by potassium bromide.

It has been employed in epilepsy, and to relieve nervousness. It is useful in headache and singing in the ears, either idiopathic or due to the administration of quinine or of iron. It is used also to remove the bad effects of excess in tea or alcohol, and to quiet palpitation.

Syrupus Acidi Hydriodici, U.S.P. Syrup of Hydriodic Acid.—A liquid containing 1 per cent. of pure hydriodic acid (HI; 127·6), sugar, and spirit of orange.

Characters.—A transparent, colourless, or not more than straw-coloured, liquid, odourless, and having a sweet acidulous taste. Sp. gr. 1·300.

Tests.—If bisulphide of carbon be poured into a small portion of the syrup and a little chlorine water added, the disulphide will separate with a violet colour in shaking. Gelatinised starch should not give to the syrup more than a faint bluish tinge; and the precipitate by silver nitrate ought to be insoluble in ammonia. 31·9 grammes of the syrup require, for complete precipitation, 25 cubic centimetres of the standard solution of nitrate of silver.

Dose.—1 to 4 fluid drachms.

Action and Uses.—Hydriodic acid may be given in asthma and bronchitis instead of iodide of potassium, to which its action is similar (p. 560).

Acidum Nitricum, B. and U.S.P. Nitric Acid. HNO_3; 63.—An acid prepared from nitrate of potassium or nitrate of sodium by distillation with sulphuric acid and water, and containing 70 per cent. B.P., or 69·4 U.S.P., by weight of nitric acid, HNO_3, corresponding to 60 per cent. of anhydrous nitric acid, N_2O_5.

Characters.—A colourless liquid, having a specific gravity of 1·42. Boiling-point, 250° F. When exposed to the air it emits an acrid, corrosive vapour.

Reactions.—If it be poured over copper-filings, dense, red vapours are immediately formed; but if the acid be mixed with an equal volume of water, and then added to the copper, it gives off a colourless gas, which acquires an orange-red colour as it mixes with the air, and which, if it be introduced into a solution of sulphate of iron, communicates to it a dark purple or brown colour, due either to solution of N_2O_2 in the sulphate or combination with it. If submitted to distillation the product continues uniform throughout the process.

Impurities.—Weaker or stronger acid, sulphuric or hydrochloric acids, fixed impurities.

TESTS.—It leaves no residue when evaporated to dryness (no fixed impurities, as iron, lead, &c.). Diluted with six times its volume of distilled water it gives no precipitate with chloride of barium or nitrate of silver (absence of sulphuric or hydrochloric acids).

PREPARATIONS CONTAINING FREE NITRIC ACIDS.

B.P.	DOSE.	U.S.P.
Acidum Nitricum Dilutum (acid 1, with about 4 of water by measure)	10–30 m.	Acidum Nitricum Dilutum (acid 1, water 6 by weight; $1\frac{1}{2}$, and $12\frac{1}{2}$ by measure).
Acidum Nitro-hydrochloricum Dilutum		Acidum Nitrohydrochloricum.
		,, ,, ,, Dilutum.
Liquor Ferri Pernitratis		
,, Hydrargyri Nitratis Acidus		
Unguentum Hydrargyri Nitratis		

ACTION.—It is an exceedingly powerful **caustic**, and destroys the tissues, but, unlike sulphuric acid, it forms, to some extent, a barrier to its own action by coagulating the albumin with which it meets. When swallowed, it may not only produce the symptoms of irritant poisoning already described (p. 395), but the vapour, getting into the larynx, may cause spasm of the glottis, and death from suffocation, or may produce intense bronchitis.

USES.—Nitric acid is applied externally to destroy chancres, warty growths, and hæmorrhoids; to the surface of phagedænic ulcers; and to bites of snakes or rabid dogs, in order to destroy the virus and prevent its absorption. Internally the dilute acid is used to quench thirst in febrile conditions, like other dilute acids, and it is useful in cases of dyspepsia. It is supposed to have an action upon the liver, and certainly appears to be of use in cases of so-called biliousness. When absorbed it has an **astringent** action, and is exceedingly serviceable in diminishing the secretion from the lungs in bronchitis and in the sub-acute exacerbations of phthisis. It is also employed in cases of syphilis occurring in debilitated subjects, where mercurials are not well borne. It diminishes the phosphatic deposits in the urine, and, in a dilute condition, has been injected into the bladder in order to dissolve calculi already formed.

U.S.P. Acidum Nitrohydrochloricum. NITROHYDROCHLORIC ACID.

CHARACTERS.—A golden yellow, fuming, and very corrosive liquid, having a strong odour of chlorine and a strongly acid reaction. By heat it is wholly volatilised. It readily dissolves gold leaf, and a drop added to a test solution of iodide of potassium liberates iodine abundantly.

PREPARATION.—By mixing nitric acid (4) with hydrochloric acid (15 parts), and, when effervescence has ceased, preserving it in glass-stoppered bottles, which should not be more than half-filled and kept in a cool place.

Acidum Nitrohydrochloricum Dilutum, B. and U.S.P. DILUTE NITROHYDROCHLORIC ACID.—It contains free chlorine,

hydrochloric, nitric, and nitrous acids and other compounds, dissolved in water.

Preparation.—By mixing nitric acid 3, hydrochloric 4, water 25, by measure, and allowing it to stand for 14 days before it is used, B.P. By diluting nitrohydrochloric acid (1) with water (26 parts by weight, U.S.P.). The proportions of the components U.S.P. are, by measure, nitric acid 3, hydrochloric acid 13½, water 80.

Dose.—5 to 20 minims.

Use.—This, like nitric acid, is supposed to have a special action upon the liver. It is sometimes used, in the form of baths or compresses, in hepatic disorders, and is frequently given in

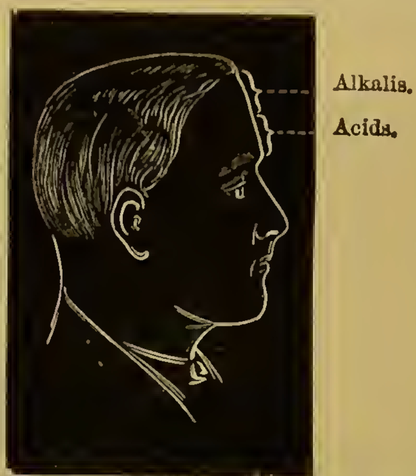

Fig. 165.—Showing the position of the frontal headaches relieved by acids and alkalis in the absence of constipation. The lower is relieved by acids, the upper by alkalis before meals. The lower one also indicates the occasional position of headache caused by straining the eyes.

cases of dyspepsia, biliousness, and jaundice. When given before meals it seems to check acidity in the stomach, and it is very useful in removing headache situated in the forehead, just above the eyebrows, and unaccompanied by constipation (Fig. 165). If the ordinary diluted acid fails, a few drops of the strong acid diluted with water at the time it is taken may succeed, and if this fails a mixture evolving oxides of nitrogen and oxides of chlorine may prove successful.[1]

Acidum Aceticum, B. and U.S.P. Acetic Acid. $HC_2H_3O_2$; 60.—An acid liquid prepared from wood by destructive distillation and subsequent purification. 100 parts by weight contain 33 B.P., 36 U.S.P., parts of acetic acid $HC_2H_3O_2$; 60 corresponding to 28 parts of anhydrous acetic acid, $C_4H_6O_3$.

Characters.—A colourless liquid having a strong acid reaction

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[1] Such a mixture is:

℞ Solutionis Sodii Nitritis (1 in 4).
Sol. Potassii Chloratis (1 in 4), āā ℥ij.
Misce.
℞ Acidi Hydrochlorici Diluti.
Aquæ, āā ℥ij.

One teaspoonful of each mixture to be added to a wineglassful of water and taken after meals.– Cook, *Practitioner*, vol. xxvii. p. 328.

and a pungent odour. Specific gravity 1·044 B.P., 1·048 U.S.P., at 15° C.

IMPURITIES.—Lime, lead, copper, tin, sulphuric and hydrochloric acids, and sulphurous acid due to the action of organic matter on the sulphuric acid.

TESTS.—It leaves no residue when evaporated (no lime, &c.), and gives no precipitate with sulphuretted hydrogen (no metals), chloride of barium (absence of sulphuric acid), or nitrate of silver (absence of hydrochloric acid). If a fluid drachm of it mixed with half an ounce of distilled water and half a drachm of pure hydrochloric acid be put into a small flask with a few pieces of granulated zinc, and while the effervescence continues a slip of bibulous paper wetted with solution of subacetate of lead be suspended in the upper part of the flask above the liquid for about five minutes, the paper will not become discoloured (absence of sulphuric acid, $SO_2 + 6H = H_2S + 2H_2O$).

PREPARATIONS CONTAINING FREE ACETIC ACID.

B.P.	STRENGTH.	DOSE.
Acetum	4·6 per cent. anhydrous acetic acid	1 fl. dr. to 1 fl. oz.
,, Cantharidis		
,, Scillæ		15 to 40 min.
Acidum Aceticum Glaciale	84 per cent. anhydrous acid.	
,, **Aceticum**	28 ,, ,, ,, ,,	
,, ,, **Dilutum**	3·6 ,, ,, ,, ,,	1 fl. dr. to 1 fl. oz.
Extractum Colchici Acetum		
Linimentum Terebinthinæ Aceticum (p. 516)	1 volume acetic acid in 3.	
Liquor Epispasticus	1 volume acetic acid in 5.	
Mistura Creasoti		
Oxymel		1 to 2 fl. dr.
,, Scillæ		½ to 1 fl. dr.
Syrupus ,,		½ to 1 fl. dr.
Tinctura Ferri Acetatis		5 to 30 min.

U.S.P.	DOSE.
Acetum Lobeliæ	30 min. to 1 fl. dr. (2 to 4 gm.)
,, Opii	4 to 15 min. (0·25 to 1 c.c.)
,, Sanguinariæ	15 to 30 min. (1 to 2 gm.) as emetic, 3 to 4 fl. dr. (12 to 16 gm.)
,, Scillæ	15 min. to 1 fl. dr. (1 to 4 gm.)
Acidum Aceticum	
,, ,, dilutum	
,, ,, glaciale	
Extractum Colchici Radicis	½ to 2 gr. (0·03 to 0·12 gm.)
Syrupus Scillæ	15 min. to 1 dr. (1 to 4 c.c.)
Tincture Ferri Acetatis	15 min. to 1 dr. (1 to 4 c.c.)

Acidum Aceticum Dilutum, B. and U.S.P. DILUTED ACETIC ACID.—Acetic acid, 1 part diluted with water 7 parts, B.P., or acid 17, water 83, U.S.P.

PROPERTIES, IMPURITIES.—The same as of acetic acid, except so far as they are affected by its dilution.

DOSE.—1 to 2 fluid drachms.

PREPARATIONS IN WHICH DILUTED ACETIC ACID IS USED.

B.P.

Acetum Scillæ. Liquor Morphinæ Acetatis.

Acidum Aceticum Glaciale, B. and U.S.P.—GLACIAL ACETIC ACID, $HC_2H_3O_2$; 60. Concentrated acetic acid, corresponding to at least 84 per cent. of anhydrous acid, $C_4H_6O_3$, B.P. Nearly or quite absolute acetic acid, U.S.P.

CHARACTERS AND REACTIONS.—It crystallises when cooled to

34° F., and remains crystalline until the temperature rises to above 48° F. Specific gravity 1·065 to 1·066, and this is increased by adding ten per cent. of water. At the mean temperature of the air it is a colourless liquid, with a pungent acetous odour, B.P.

At or below 15° C. (59° F.) a crystalline solid; at a higher temperature, a colourless liquid. When liquefied and as near as possible to 15° C. (59° F.) it has the sp. gr. 1·056–1·058. Its properties are similar to those of acetic acid, and it is similarly affected by reagents. U.S.P.

PREPARATIONS IN WHICH GLACIAL ACETIC ACID IS USED.

B.P.

Acetum Cantharidis. Mistura Creasoti.
Linimentum Terebinthinæ Aceticum (p. 516).

B.P. Acetum. VINEGAR.—An acid liquid, prepared from malt and unmalted grain by the acetous fermentation.

CHARACTERS.—A liquid of a brown colour and peculiar odour.

IMPURITIES.—A little sulphuric acid added to it is said to make it keep better. Too much may be fraudulently added in order to increase its acidity. Lead from the vessels in which it is kept.

TESTS.—If ten minims of solution of chloride of barium be added to a fluid ounce of the vinegar, and the precipitate, if any, be separated by filtration, a further addition of the test will give no precipitate (limit of sulphuric acid). Sulphuretted hydrogen causes no change of colour (absence of lead).

DOSE.—1 to 2 fluid drachms.

PREPARATION IN WHICH VINEGAR IS USED.

Emplastrum Saponis Fuscum.

ACTION AND USES.—When applied externally to the skin, glacial acetic acid causes the formation of a large bleb. It is used to destroy warts and corns, and is sometimes employed as a **vesicant** in cases of kidney-disease, where danger is apprehended from the use of cantharides. When the vapour of it is sniffed up the nose, it causes reflex contraction of the blood-vessels, and raises the blood-pressure. It is therefore useful in lessening drowsiness and preventing syncope, or arousing patients from it (pp. 194 and 265).

Dilute acetic acid is applied to the skin in cases of headache, and is used to sponge the surface and check perspiration when too profuse. It checks bleeding, and may be used to stop oozing from leech-bites, or to wash out the mouth after the extraction of a tooth, and, when sniffed up the nose, sometimes arrests epistaxis. It is occasionally employed in the form of an enema to destroy ascarides.

When applied either alone or mixed with proof spirit on a napkin to the vulva it is sometimes very useful in checking menorrhagia (*vide* p. 351).

Acidum Phosphoricum Concentratum, B.P., Acidum

Phosphoricum, U.S.P. Phosphoric Acid.—Phosphoric acid, H_3PO_4, with 33·7 per cent. of water, B.P. A liquid composed of 50 per cent. of ortho-phosphoric acid (H_3PO_4; 98) and 50 per cent. of water, U.S.P.

Characters.—A colourless syrupy liquid, without odour, and of a strongly acid taste and reaction, sp. gr. 1·347. When heated it loses water, and when a temperature of about 200° C. (392° F.) has been reached, the acid is gradually converted into pyro-phosphoric and metaphosphoric acids, which may be volatilised at a red heat.

Preparation.—Oxidising phosphorus by nitric acid. *Vide* p. 567.

Reactions.—When diluted, and supersaturated with ammonia, the test-solution of magnesium gives a white precipitate. *Vide* also the reactions and tests of acidum phosphoricum dilutum.

Preparations containing Free Phosphoric Acid.

B.P.	U.S.P.
Acidum Phosphoricum Dilutum.	Acidum Phosphoricum Dilutum.
Syrupus Ferri Phosphatis.	

Acidum Phosphoricum Dilutum, B. and U.S.P. Diluted Phosphoric Acid.—Concentrated phosphoric acid, 3 parts mixed with water up to 20 parts; forming a solution corresponding to 10 per cent. by weight of phosphoric anhydride, P_2O_5, B.P.

Phosphoric acid 20 parts with 80 of water, U.S.P.

Characters.—A colourless liquid, with a sour taste and strongly acid reaction. Specific gravity, 1·08.

Reactions.—With ammonio-nitrate of silver it gives a canary-yellow precipitate, soluble in ammonia and in diluted nitric acid. Evaporated, it leaves a residue which melts at a low red heat, and upon cooling exhibits a glassy appearance.

Impurities.—Phosphorous acid, meta- and pyro-phosphoric acids, nitric, sulphuric, and hydrochloric acids, arsenic.

Tests.—It is not precipitated by sulphuretted hydrogen (no metals), chloride of barium (no sulphuric acid), nitrate of silver acidulated with nitric acid (no hydrochloric acid), nor by the solution of albumin (absence of meta-phosphoric acid which coagulates albumin). When mixed with an equal volume of pure sulphuric acid, and then introduced into solution of sulphate of iron, it does not communicate to it a dark colour (absence of nitric acid). Mixed with an equal volume of solution of perchloride of mercury and heated, no precipitate is formed (no pyro-phosphates). Its strength is estimated gravimetrically by ascertaining the increase in weight which occurs in oxide of lead when phosphoric acid is poured on it, evaporated and ignited.

Dose.—10–30 minims.

Uses.—Phosphoric acid may be used to allay thirst, like other dilute acids, in febrile states, and in diabetes. It may be given in larger doses than other mineral acids without deranging digestion, and is therefore to be preferred to them in cases where it requires to be given for a length of time, as in diabetes and alkalinity of the urine. It is said to be useful in scrofula, and to diminish the growth of bony tumours.

Acidum Tartaricum, B. and U.S.P. TARTARIC ACID. $H_2C_4H_4O_6$; 150.—A crystalline acid prepared from the acid tartrate of potassium.

CHARACTERS.—In colourless crystals, the primary form of which is the oblique rhombic prism. It has a strongly acid taste, and is readily soluble in water and in rectified spirit. When to either solution, not too much diluted, a little acetate of potassium is added, a white crystalline precipitate is formed.

$$20 \text{ grains neutralise} \begin{cases} 27 \text{ grains bicarbonate of potassium.} \\ 22 \quad ,, \quad\quad ,, \quad\quad \text{sodium.} \\ 15\frac{1}{2} \quad ,, \quad \text{carbonate of ammonium.} \end{cases}$$

PREPARATION.—*Vide* p. 566.

IMPURITIES.—Lead, copper, and iron from the vessels in which it is prepared; calcium, or acid tartrate of potassium, from the substances used in its preparation; racemic and oxalic acids.

TESTS.—An aqueous solution of the acid is not affected by sulphuretted hydrogen (absence of metals), and gives no precipitate with the solution of sulphate of calcium (no racemic or oxalic acids), or of oxalate of ammonium (no calcium). It leaves no residue, or only a mere trace, when burned with free access of air (no acid tartrate of potassium).

DOSE.—10 to 30 grains.

ACTION AND USES.—Used for cooling drinks.

Acidum Citricum, B. and U.S.P. CITRIC ACID. $H_3C_6H_5O_7.H_2O$; 210.—A crystalline acid prepared from lemon-juice, or from the juice of the fruit of the lime, *Citrus Bergamia.*

CHARACTERS.—In colourless crystals, of which the right rhombic prism is the primary form; very soluble in water, less soluble in rectified spirit, and insoluble in pure ether. The crystals dissolve in three-fourths of their weight of cold, and in half their weight of boiling water. The diluted aqueous solution has an agreeable acid taste. When the solution is made by dissolving thirty-four grains of the acid in one ounce of water, it resembles lemon-juice in strength and in the nature of its acid properties, and, like lemon-juice, it undergoes decomposition and becomes mouldy by keeping.

The quantity contained in $\frac{1}{2}$ fl. oz. of this solution, viz. :—

$$17 \text{ grains neutralises} \begin{cases} 25 \text{ grains bicarbonate of potassium.} \\ 20 \quad ,, \quad\quad ,, \quad\quad \text{sodium.} \\ 15 \quad ,, \quad \text{carbonate of ammonium.} \end{cases}$$

PREPARATION.—*Vide* p. 566.

IMPURITIES.—Lead and copper from the vessels in which it is prepared, calcium used in its preparation, tartaric acid, which is cheaper, and is apt to be mixed with or substituted for it, sulphuric acid or sulphates, oxalic acid.

TESTS.—The aqueous solution is not darkened by sulphuretted hydrogen (absence of metals), gives no precipitate when added in excess to solution of acetate of potassium (no tartaric acid), or of chloride of barium (no sulphates), and if sparingly added to cold lime-water it does not render it turbid (no oxalic acid). The crystals leave no ash when burned with free access of air (no calcium).

DOSE.—10 to 30 grains.

PREPARATIONS CONTAINING FREE CITRIC ACID.

B.P.	U.S.P.
Succus Limonis.	Syrupus Acidi Citrici.
Syrupus Limonis.	„ Limonis.
Vinum Quininæ.	

U.S.P. Syrupus Acidi Citrici. SYRUP OF CITRIC ACID.—Citric acid 8, water 8, spirit of lemon 4, syrup 980.

ACTION AND USES.—Citric acid, from the agreeable taste of its solution in water, is used for drinking in fever to allay thirst, either alone or with alkaline bicarbonates as effervescing drinks. It is also used in scurvy, as it is supposed by some to be the ingredient to which lemon-juice owes its curative properties in that disease.

B.P. Oxalic Acid, Purified. $H_2C_2O_4 . 2H_2O$; 126.

Dissolve 1 pound of commercial oxalic acid in 30 fluid ounces of boiling distilled water, filter the solution, and set it aside to crystallise. Pour off the liquor, and dry the crystals by exposure to the air on filtering paper placed on porous bricks.

TEST.—It is entirely dissipated by a heat below 350° F.

USES.—As a test.

Standard Solution of Oxalic Acid, B.P. and U.S.P.—63 grammes dissolved in water to 1000 c.c.

Acidum Boricum, B. and U.S.P. BORIC OR BORACIC ACID. H_3BO_3; 62.

CHARACTERS.—Transparent, colourless, six-sided plates, slightly unctuous to the touch, permanent in the air, odourless, having a cooling, bitterish taste and a feebly acid reaction; in solution turning blue litmus-paper red and turmeric paper brown, the tint in the latter case remaining unaltered in presence of free hydrochloric acid. The alcoholic solution burns with a flame tinged with green.

PREPARATION.—*Vide* p. 566.

IMPURITIES.—Sulphates, chlorides, lead, copper, iron, &c., calcium and sodium salts.

TESTS.—An aqueous solution of boric acid should not be precipitated by test solutions of chloride of barium, nitrate of silver with nitric acid, sulphide of ammonium, or oxalate of ammonium. A fragment heated on a clean platinum wire in a non-luminous flame should not impart to the latter a persistent yellow colour.

DOSE.—5–30 grains.

OFFICINAL PREPARATION.

B.P.

Unguentum Acidi Borici.—Boric acid 1, soft paraffin 4, hard paraffin 2.

ACTION AND USES.—From its power of turning turmeric brown it is used as a test for this substance in rhubarb. It has the power of destroying low organisms, and has therefore been used as an **antiseptic** application to wounds either in the form of a solution (1 part in 20 of hot water) or of an ointment. The antiseptic ointment originally recommended by Lister consisted

of a mixture of the acid (1) with white wax (1), paraffin (2), almond oil (2). This is rather hard, and a better ointment consists of the powdered acid (3), paraffin (5) and vaseline (10). The relative proportions of these may be varied according to the temperature, more or less paraffin being added according as the temperature is high or low. Boric acid lint is a useful antiseptic dressing for small wounds and ulcers; and as an antiseptic hot fomentation in small abscesses, whitlows, &c. The powdered acid, mixed with starch, forms a useful dusting powder for infants, and lessens the fœtor of perspiration. When given internally it is said to be occasionally useful in cases of vomiting in somewhat the same way as sulphurous acid, and it has also been given along with ether in septic diseases. **Boro-glyceride**, discovered and patented by Barff, is made by heating 92 parts of glycerine with 62 of boric acid. A solution of 1 in 40 of water is recommended as a powerful antiseptic. It is used to preserve food, and as a lotion for the treatment of wounds and in purulent ophthalmia.[1]

Acidum Chromicum, B. and U.S.P. CHROMIC ACID, CrO_3; 100·4. It is an anhydride (not a true acid).

CHARACTERS.—Small, crimson, needle-shaped or columnar crystals, deliquescent, odourless, having a caustic effect upon the skin and other animal tissues, and an acid reaction. Very soluble in water, forming an orange-red solution. Brought in contact with alcohol, mutual decomposition takes place. When heated to about 190° C. (374° F.) chromic acid melts and at 250° C. (482° F.) it is mostly decomposed, with the formation of dark green chromic oxide and the evolution of oxygen. On contact, trituration, or warming with strong alcohol, glycerine, spirit of nitrous ether, or other easily oxidisable substances, it is liable to cause sudden combustion or explosion.

TESTS.—If 1 grain of chromic acid be dissolved in 100 c.c. of cold water and mixed with 10 c.c. of hydrochloric acid, the further addition of 1 c.c. of test solution of chloride of barium should cause not more than a white turbidity (limit of sulphuric acid).

OFFICINAL PREPARATION.

B.P.

Liquor Acidi Chromici (acid 1, water 3 parts).

ACTION.—It has a great power of coagulating albumin, and destroying low organisms, and as it parts very readily with oxygen it oxidises organic matter and decomposes ammonia and sulphuretted hydrogen. It is thus a powerful deodoriser and **disinfectant**. It is chiefly used as a **caustic** to destroy condylomata, and morbid growths in the mouth, larynx, or uterus, and to phagedænic ulcers, poisoned wounds, &c. As a solution of 1 in 40, it has been especially recommended in syphilitic affections of

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[1] *Extra Pharmacopœia*, Martindale and Westcott.

the tongue, mouth, and throat. As a lotion, it has been employed to lessen fœtid discharges, and as an injection in ozæna, leucorrhœa and gonorrhœa. Care must be taken not to prescribe it with any substance to which it readily yields oxygen, such as alcohol, glycerine, &c., as the mixture may explode spontaneously.

Acidum Carbonicum. CARBONIC ACID, CO_2; 44. Not official. It is very extensively used dissolved in water, as aërated water, effervescing soda, potash, or lithia waters, or in wine, as champagne.

PROPERTIES.—Colourless gas, heavier than air, causing a pungent feeling in the nostrils. Soluble in its own volume of water. Its solubility is increased by the presence of carbonates, or by pressure, and when this is removed the gas escapes and causes the fluid to effervesce. The solution has an acid reaction. Carbonates of magnesium, calcium, iron, &c., which are only sparingly soluble in water, are dissolved with comparative ease by water holding the gas in solution.

ACTION AND USES.—Like other acids, when applied to the **skin** it acts as an irritant, but only slightly. After a prolonged application it causes a slight reddening of the skin and a feeling of warmth, which changes on the continuance of the application into burning or prickling, felt most where the skin is thin and richly supplied with nerves, as the external genitals, and this is not unfrequently accompanied by sweating. Carbonic acid baths (p. 469) are therefore sometimes used in catarrh and rheumatism as a slight rubefacient to the whole skin, and to cause sweating, especially where they can be obtained with ease, as in places where there are springs containing much carbonic acid. These baths —e.g. the ferruginous carbonic acid baths of various continental spas—have an aphrodisiac action and may be useful in sterility.

Carbonic acid has been used as a stimulant to ulcers, either by directing a stream of gas directly upon them or by applying a poultice of yeast (Cataplasma Fermenti, B.P.), which in the process of fermentation causes a constant production of this gas.

Streams of carbonic acid have been applied to the eyes, ears, nose, vagina, and rectum in catarrhal inflammation or ulceration of these parts, in order to cause a slight hyperæmia of the parts and healing of the inflammation and to diminish pain, as it is supposed to act locally by diminishing the sensibility of the nerves of the part.

In the **mouth** carbonic acid, like other acids, acts as a stimulant to the secretion of saliva, and so water containing it quenches thirst better than pure water, and it is therefore often used in feverish states (p. 360).

In the **stomach** it causes that slight pain which we confound with hunger, and a pleasant feeling of warmth just as on the skin. Here too it most probably causes a slight hyperæmia, and

increased secretion. The greatest part leaves the stomach as gaseous eructations, but a portion is absorbed and enters the blood. Its action is thus transient, and it produces no material change in the chemical composition either of the contents or walls of the stomach. It increases the rapidity of the absorption of water in the **intestinal canal**, as is shown by the fact that water containing carbonic acid is excreted by the kidneys much sooner after it has been drunk, than water without it. It relieves irritation in the stomach, and allays or stops vomiting or nausea and slight derangements of digestion. Carbonic acid is naturally present in the intestines, in greater quantities in the large than the small. The carbonic acid is partly that which passes from the blood into the intestine in interchange for the oxygen contained in the air we swallow, and is partly formed by processes of fermentation which take place in the chyme.

That part of the carbonic acid which, after introduction into the stomach, passes into the blood is excreted by the lungs. Injected into the blood through a vein, it is likewise excreted in the same way without causing an injury, unless it is injected in such a quantity that some remains as gas undissolved in the blood, and then it causes death mechanically, just like air, by hindering the passage of blood through the lungs.

Poisoning by Carbonic Acid.—When it is inhaled, the ordinary interchange between the carbonic acid in the blood and the oxygen of the air is prevented, the gas in the blood accumulates, and the processes of oxidation in tissues being interfered with, their functions are lessened or destroyed (p. 262).

The nervous system is first affected, and there is headache, beating or singing in the ears, giddiness, flushing of the face. Then there is a feeling of want of breath, tightness of the breast, palpitation of the heart and great anxiety. If the CO_2 be still inhaled, the pulse becomes slower, consciousness is lost, delirium or coma ensues, and death occurs with convulsions.

In poisoning by carbonic acid three stages may be distinguished, (1) dyspnœa; (2) convulsions; (3) paralysis.

During the first stage the carbonic acid appears to act as a stimulus to the nerve-centres in the medulla, and especially to the respiratory and vaso-motor centres. In the second stage it stimulates other motor centres (p. 237). In the third it paralyses them. In the first stage, that of **dyspnœa**, the respirations are both rapid and deep, the inspiratory as well as the expiratory movements being increased. Both the inhibitory and the accelerating centres for the heart are stimulated, but the irritation of the vagus-roots preponderates, and the heart is generally slow. The vaso-motor centre in the medulla is also stimulated, and the blood-pressure rises. Besides this the carbonic acid also stimulates either subsidiary centres in the spinal cord (pp. 285 and 286), or acts directly on the walls of the vessels themselves, causing them

to contract (p. 282), for the blood-pressure rises during inhalation of carbonic acid even when the spinal cord has been divided below the medulla. The vessels of the surface become dilated. This is ascribed by Frankel to stimulation of a dilating centre. During the second stage, that of **convulsions**, the respiration becomes more and more laboured, and the expiratory movements greater, until general convulsions occur. The blood-pressure rises still more, the heart becomes still slower, and the right ventricle more distended. In the third stage, that of **paralysis**, the inspiratory movements become more and more feeble, the intervals between them longer and longer, and finally they cease. The vaso-motor centre becoming exhausted the blood-pressure falls, and this fall is probably aided by the action of the carbonic acid on the muscular walls of the blood-vessels themselves (p. 282), as well as by weakness of the heart. The heart generally continues to beat for some minutes after respiration has completely ceased, and if artificial respiration be commenced before pulsation is entirely arrested, life may generally be saved. Indeed, this is the case even when the cardiac pulsations are quite imperceptible, and therefore in cases of death from asphyxia it is well to keep up artificial respiration if possible for an hour or even longer, notwithstanding the apparent hopelessness of the case. It should only be discontinued when a ligature tied moderately tightly causes no trace of congestion in the finger-tip after being on for ten minutes, and it ought to be supplemented by intermittent pressure on the cardiac region in order to stimulate the heart. These observations apply not only to poisoning by carbonic acid, but to poisoning by all drugs which produce death by asphyxia, and to death by drowning.

Post-mortem examination shows great venous congestion everywhere, the right side of the heart being distended with blood, the brain much congested, with exudation and even extravasation, and the blood extraordinarily dark.

TREATMENT.—In cases of poisoning by carbonic acid, as in miners or men who have been suffocated in wells or brewers' vats, the great object is to get the blood oxygenated as quickly as possible. Get the person into the fresh air, and if the respiratory movements have ceased, dash cold water on the face and chest to awaken them reflexly. If this does not do, have recourse to artificial respiration. The next thing is to see that the heart is beating. When the right ventricle is distended with blood it becomes paralysed, and if it does not begin to beat shortly after artificial respiration has been begun the jugular vein should be opened in order to relieve the dilatation. There are no valves between the heart and the jugular vein (at least of any importance), so the blood flows directly out and the distended ventricle is relieved. One must, of course, be careful to prevent the access of air into the vein.

Acidum Hydrocyanicum Dilutum, B. and U.S.P. Diluted Hydrocyanic Acid. Prussic Acid.—Hydrocyanic acid, HCN, dissolved in water, and constituting 2 per cent. by weight of the solution, B.P. A liquid consisting of 2 per cent. of absolute hydrocyanic acid (HCN ; 27) and 98 per cent. of water, U.S.P.

Characters.—A colourless liquid with a peculiar odour. Specific gravity, 0·997. It only slightly and transiently reddens litmus-paper.

Reaction.—Treated with a minute quantity of a mixed solution of sulphate and persulphate of iron, afterwards with potash, and finally acidulated with hydrochloric acid, it forms Prussian blue.

Preparation.—By distilling yellow prussiate of potash with H_2SO_4.

$$\underset{\text{Potassium Ferrocyanide}}{2K_4FeCy_6} + 6H_2SO_4 = 6HCy + \underset{\text{Everett's Yellow Salt}}{K_2Fe_2Cy_6} + 6KHSO_4.$$

Half the cyanogen of the ferrocyanide passes over as hydrocyanic acid, while a ferrocyanide of potassium and iron, often called Everett's yellow salt, remains behind along with potassium sulphate.

Impurities.—The most important is want of strength, so that when prescribed it has not the desired effect. It loses strength when kept, and therefore the volumetric test is more important than in the case of other acids.

Tests.—A fluid drachm of it evaporated in a platinum dish leaves no fixed residue (no fixed impurities). It gives no precipitate with chloride of barium (no sulphuric acid), but with nitrate of silver it gives a white precipitate entirely soluble in boiling concentrated nitric acid (no hydrochloric acid). 270 grains of it rendered alkaline by the addition of solution of soda, require 1,000 grain-measures of the volumetric solution of nitrate of silver to be added before a permanent precipitate begins to form, which corresponds to 2 per cent. of the real acid. Silver nitrate forms a soluble double cyanide of silver and sodium, and till all the hydrocyanic acid is used up no silver oxide is precipitated. $AgNO_3 + 2NaCy = NaNO_3 + NaAgCy_2$. The silver oxide reacts on the soluble compound, and decomposes it, so that a permanent precipitate of silver cyanide is formed. $2NaAgCy_2 + Ag_2O + H_2O = 2NaHO + 4AgCy$.

Standard silver test solution contains $\frac{1}{10}$ of an equivalent of $AgNO_3$, and 1,000 grains therefore combine with $\frac{1}{10}$ of 2NaCy.

Dose.—2 to 8 minims. As a lotion, 5–10 min. to 1 fl. oz. of water, rose water, elderflower water, or almond mixture. The addition of 1 fl. dr. of glycerine tends to prevent evaporation.

Preparations. **B.P.**

Vapor Acidi Hydrocyanici.

Tinctura Chloroformi et Morphinæ (contains 1 vol. in 16).

B.P. Vapor Acidi Hydrocyanici. Vapour of Hydrocyanic Acid.—Mix 10 to 15 minims of diluted hydrocyanic acid with 1 fluid drachm of cold water in a suitable apparatus, and let the vapour that arises be inhaled.

Action.—Hydrocyanic acid differs from all the other acids in having upon the organism an action peculiarly its own. It is one of the most powerful and most rapid poisons known. It destroys protoplasmic movement, kills infusoria, checks oxidation, and arrests fermentation. When applied to the skin it passes through the epidermis and paralyses the ends of the sensory nerves below, so that the part becomes numb, and tactile

sensation is diminished or destroyed. It is rapidly absorbed from the mucous membranes, and its action is the same when applied to any of them. A single drop of pure hydrocyanic acid injected into the eye, nose, or mouth of a small animal causes it to fall down dead as if struck by lightning, and the same dose is sufficient to cause the death even of a large animal. In these cases the pupils are usually widely dilated, and the animal generally utters a characteristic cry. When a smaller, but still fatal dose is given, the **poisoning** may be divided into three stages. In the **first** stage the **brain** is chiefly affected. There is giddiness, uncertain gait, a few slow breaths, and then rapid respiration and irregular action of the heart. These are succeeded in the **second** stage by violent **convulsions**, tonic and clonic. The head is bent backwards, the limbs are stiffly extended, and sensibility is generally lost, although reflex action may still persist. In the **third** stage there is **coma**, complete loss of sensibility, paralysis of the voluntary muscles, almost imperceptible pulse, slow and weak respiration—the expiratory movements predominating, and death.

It is evident that these are the symptoms of rapid **asphyxia** They are very like those produced by carbonic acid, but much more rapid, and resemble those of poisoning by sulphuretted hydrogen. The convulsions occur only in warm-blooded animals, and not in frogs. In this point they resemble those of simple asphyxia (p. 237). They differ from those of ordinary asphyxia, however, in the fact that whereas the blood is venous when asphyxial convulsions occur, the blood is arterial in colour when the hydrocyanic acid convulsions occur. They differ also in not being arrested by artificial respiration.

Death, in animals poisoned by hydrocyanic acid, is due to sudden arrest of the **heart** in the more rapid cases, and to paralysis of the **respiration** in those which occur more slowly. In consequence of this, the blood in the left side of the heart is found to be arterial in cases of instantaneous death, but venous in those instances where some minutes have been required. It is stated that in the first stage of poisoning the blood is more arterial than usual, though it afterwards becomes more venous. This has been said to depend upon diminution of the oxidising power of the **blood** by the action of the acid. Hydrocyanic acid is said to form a compound with hæmoglobin (cyan-hæmoglobin) which does not readily give up its oxygen (p. 70). But this compound is often not to be found in the blood of animals poisoned by the acid, and the arterial appearance is more probably due to dilatation of the peripheral vessels allowing the blood to pass through them rapidly, without undergoing the usual changes, just as it does in the sub-maxillary gland on irritation of the chorda tympani nerve. This is rendered all the more probable by the fact, that at the exact moment in which the blood becomes

of an arterial colour in the veins, the blood-pressure suddenly falls in the arteries (Rossbach).

The **respiratory changes**, however, do seem to be also interfered with, for in the first stage of poisoning the exhalation of carbonic acid is diminished. As the diminution in the power of the blood to give oxygen off is hardly sufficient to explain this, and as the convulsions, apparently asphyxial in character, come on while the blood is still arterial, we may, with some probability, suppose that the respiratory changes are due to the effect of the hydrocyanic acid in lessening internal respiration in the nervous tissues themselves (p. 239).

The stoppage of the **heart** in mammals is partly due to irritation of the vagus-roots in the medulla, and partly to paralysis of the motor ganglia in the heart.

When placed upon the heart of a frog it arrests its beats, but the heart, at first, still contracts when irritated, though after a short time its muscular irritability is also lost.

That its action in stopping the mammalian heart is partly due to irritation of the vagus-roots is shown by the fact that, in some animals, section of the vagi prevents the stoppage. The effect of hydrocyanic acid is, first to raise, and afterwards greatly to depress the **arterial pressure**, and at the same time to slow the **pulse**. The slowing and paralysis of respiratory movements which this acid produces are chiefly due to its action on the **respiratory centre** in the medulla oblongata. When directly applied to the medulla in the alligator it causes continuous powerful expiration and death, whereas when given in other ways considerable time is required for its action to be produced. It appears to paralyse the **brain**, peripheral **afferent nerves**, then **spinal cord, motor nerves**, and **muscles**. That the afferent nerves are paralysed before the cord is proved by the fact that when frogs are poisoned with prussic acid, and afterwards with strychnine, slight irritation of the sensory nerve-roots will cause tetanus, after irritation of the periphery has ceased to produce any effect.

This fact was observed by Von Kiedrowski, working under Reichert's direction. The same author observed the effect of the local application of hydrocyanic acid in paralysing muscle and nerve, by removing the soft parts and bones from the lower part of the thigh of a frog, leaving the leg attached to the body only by nerves (Fig. 166). The grastrocnemius and crural muscles were then separated, and the gastrocnemius with its nerve was immersed in aqueous humour diluted with water, and the crural muscles with their nerves in a similar liquid to which hydrocyanic acid had been added. After four hours the crural muscles did not contract on direct irritation, but the gastrocnemius did so readily. This showed that the acid had paralysed the **muscles**. Irritation of the gastrocnemius, of its nerve *f g*, or of the sciatic nerve *a*,

caused reflex movements in the body of the frog, but irritation of the crural muscles caused no such reflex movements, showing that the ends of the sensory nerves within them had been paralysed. When the sciatic *a* was irritated the crural muscles did not contract, but the gastrocnemius did. The poison probably paralyses motor nerves as well as muscles, for it is found that the muscles contract, though feebly, on direct irritation, after they have ceased to respond to the strongest irritation of the motor nerves.

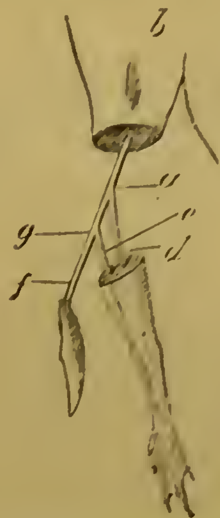

FIG. 166.—After Kiedrowski. Diagram to show the effect of hydrocyanic acid when applied locally. *a*, the sciatic nerve; *b*, thigh of a frog; *d* and *e*, branches of sciatic going to the crural muscles; *f g*, branch going to the gastrocnemius.

USES.—Hydrocyanic acid is used externally in order to lessen itching in skin-diseases, and is best applied in combination with glycerine. It is chiefly employed internally to diminish irritability of the stomach, and to relieve vomiting, also pain in the stomach or intestines, and functional palpitation of the heart dependent on dyspepsia. It is also used to relieve cough in cases of bronchitis, phthisis, asthma, and whooping cough. It has sometimes been employed, though with doubtful effect, in chorea, epilepsy, and hysteria. Its vapour is sometimes used to lessen irritability of the respiratory passages and cough.

Acidum Lacticum, B. and U.S.P. LACTIC ACID. $HC_3H_5O_3$; 90.—A liquor composed of 75 per cent. of absolute lactic acid and 25 per cent. of water.

CHARACTERS.—A nearly colourless syrupy liquid, odourless, having a very acid taste, and an acid reaction. Sp. gr., 1·212. It is freely miscible with water, alcohol and ether, but nearly insoluble in chloroform. It is not vaporised by a heat below 160° C. (320° F.); at higher temperatures it emits inflammable vapours, then chars, and is finally entirely volatilised, or leaves but a trace of residue.

PREPARATION.—By adding chalk to sour milk and decomposing the lactate of calcium with sulphuric acid (*vide* p. 566).

IMPURITIES.—Hydrochloric acid, sulphuric acid, sarcolactic acid, lead, iron, sugars, glycerin, organic impurities.

TESTS.—When diluted with water, lactic acid should afford no precipitate with test solutions of nitrate of silver, chloride of barium, sulphate of copper, nor with sulphide of ammonium after the addition of excess of water of ammonia. It should not reduce warm test-solution of potassio-cupric tartrate. When mixed and heated with excess of hydrated zinc oxide and extracted with absolute alcohol, the latter should not leave a sweet residue on evaporation. Cold concentrated sulphuric acid shaken with an equal volume of lactic acid should assume at most only a pale yellow colour.

DOSE.—1 to 3 fl. dr. per diem, diluted or sweetened, like lemonade.

When used as a **caustic** it may either be applied on lint covered with gutta percha or as a paste of silica saturated with the acid. After being left on for 12 hours it should be washed off, and the application renewed as necessary.

PREPARATION.

B.P.	DOSE.
Acidum Lacticum Dilutum (acid 3, water up to 20)......	$\frac{1}{2}$–2 fl. dr.

ACTION.—It has been employed in a solution of 1 part to 5, to dissolve the false membrane in croup and diphtheria. In cases of dyspepsia it is used to aid digestion in somewhat the same way as hydrochloric acid, and it has been given also to lessen the alkalinity of the urine and prevent phosphatic deposits. In diabetes it has been employed with considerable success along with an exclusively meat diet in doses of $\frac{1}{2}$ oz. in 1 pint of water daily, though it is said to have given rise to rheumatism in a diabetic patient. Buttermilk has been recommended in place of it, but the difficulty of obtaining this in towns is very great.

Acidum Oleicum, B. and U.S.P. OLEIC ACID.—$HC_{18}H_{33}O_2$; 282.

CHARACTERS.—A yellowish, oily liquid, gradually becoming brown, rancid and acid, when exposed to the air; odourless, or nearly so, tasteless, and, when pure, of a neutral reaction. Sp. gr., 0·800 to 0·810.

PREPARATION.—It is obtained by adding lead oxide to almond oil, which forms an oleate of lead or lead soap, and decomposing this by hydrochloric acid. Or by decomposing palm oil by superheated steam, and separating from any solid fats by pressure (*vide* p. 566).

SOLUBILITY.—Oleic acid is insoluble in water, but completely soluble in alcohol, chloroform, benzin, benzene, oil of turpentine, and the fixed oils.

At 14° C. (57·2° F.) it becomes semi-solid, and remains so until cooled to 4° C. (39·2° F.), at which temperature it becomes a whitish mass of crystals.

TESTS.—At a gentle heat the acid is completely saponified by carbonate of potassium. If the resulting soap be dissolved in water and exactly neutralised with acetic acid, the liquid will form a white precipitate with test-solution of acetate of lead. This precipitate, after being twice washed with boiling water, should be almost entirely soluble in ether (absence of more than traces of palmitic and stearic acids). Equal volumes of the acid and ot alcohol, heated to 25° C. (77° F.) should give a clear solution, without separating oily drops upon the surface (fixed oils).

USES.—Oleic acid is employed only for the preparation of oleates, which are not only elegant preparations, but appear to be more readily absorbed than other ointments.

PREPARATIONS.

B.P.

Oleatum Hydrargyri (yellow oxide of mercury 1, oleic acid 9). This oleate may be prepared with half the above proportion of oleic acid, the remainder being added just before, or not long before, the oleate is dispensed.

Oleatum Zinci (oxide of zinc 1, oleic acid 9).

Unguentum Zinci Oleati (oleate of zinc 1, soft paraffin 1).

U.S.P.	AMOUNT USED.
Oleum Hydrargyri. OLEATE OF MERCURY (Hydrargyri Oxidum Flavum, 1 part; Acidum Oleicum, 9 parts)......	10 min., externally.
Oleatum Veratrinæ. (Veratrinum, 2 parts; Acidum Oleicum, 98 parts)..	6–25 gr., externally.

Acidum Arseniosum.—*Vide* p. 719.
Acidum Benzoicum.—*Vide* p. 964.
Acidum Carbolicum.—*Vide* p. 813.
Acidum Chrysophanicum.—*Vide* p. 909.
Acidum Gallicum.—*Vide* p. 1033.
Acidum Meconicum.—*Vide* p. 846.
Acidum Pyrogallicum.—*Vide* p. 819.
Acidum Salicylicum.—*Vide* p. 819.
Acidum Tannicum.—*Vide* p. 1031.

CHAPTER XXIV.

METALS.

GENERAL CLASSIFICATION OF THE METALS.

It has already been mentioned (p. 20) that Mendelejeff's classification of the elements, although it gives us the outlines of a true natural classification, is not at present perfect, inasmuch as it separates members of natural groups, such as those of the earthy metals. In regard to this classification it must be borne in mind that by it the elements are arranged in groups according to their atomicity, and this is not in all cases determined. A glance at the table (p. 19) will show this, for copper, silver, and gold are there included both in Group I., containing monad metals, and in Group VIII. But the commonest and most stable compounds of copper, such as cupric oxide or cupric sulphide, appear to show that it is a dyad rather than a monad. Silver, also, though it appears like copper in Groups I. and VIII., may also be a dyad,[1] while gold forms two series of compounds, in one of which it is monad, and in the other triad. In the classification which I have adopted, I have followed Mendelejeff's tables as modified by Watts, but I have modified them somewhat, in order not to separate metals having a similar physiological action.

Class I.—MONAD METALS.[2]

Group I.—Alkalis—Potassium, Sodium, Lithium, *Cæsium*, *Rubidium*.

II.—Ammonium.

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[1] The formula of argentous oxide is Ag_4O, and if this formula be correct, and silver be a monad, oxygen must be a tetrad; but if silver be a dyad, argentous oxide may be represented as $\begin{array}{c}Ag-Ag\\ Ag-O-Ag.\end{array}$ (Fownes' *Chemistry*, by Watts, 12th ed. vol. i. p. 369.)

[2] The metals whose names are printed in italics are not officinal.

Class II.—DYAD METALS.

Group I.—Metals of the alkaline earths—Calcium, *Strontium*, Barium.
(Appendix.) Metals of the earths—Aluminium, Cerium, *Beryllium*, *Zirconium*, *Thorium*, *Lanthanum*, *Didymium*, *Yttrium*, *Erbium*.
II.—Magnesium.
III.—Copper, Zinc, Silver, *Cadmium*.
IV.—Mercury.

Class III.—TRIAD METALS.

Thallium, *Iridium*, *Gallium*.

Class IV.—TETRAD METALS.

Tin, Lead, *Titanium*.

Class V.—PENTAD ELEMENTS.

Nitrogen, Phosphorus, Arsenic, Antimony, Bismuth, *Vanadium*, *Tantalum*, *Niobium or Columbium*.

Class VI.—HEXAD METALS.

Chromium, *Uranium*, *Tungsten*, *Molybdenum*.

Class VII.—HEPTAD METALS.

Manganese.—*Vide* next group.

Class VIII.

Group I.—Iron metals. Iron, Nickel, Cobalt, Manganese.
II.—Platinum, Gold.

General Tests for the Acid Radicals in Metallic Salts.—As the same acids occur in the salts of different metals, the tests for their presence are described again and again in the Pharmacopœias. In order to save repetition, it may be advisable to give here in a tabular form the tests for the different acids. It is to be remembered that the same tests apply to the simple recognition of a metallic salt, and to its detection as an impurity in other substances. The tests are generally applied to solutions of the salt in water.

Salt	Reagent	Reaction
Acetate * . .	Sulphuric acid . .	Vapour of acetic acid given off and recognised by its smell.
,,	Ferric chloride .	Deep red colour.
Borate . .	Sulphuric acid . .	The saturated solution causes deposit of shining scales, which give a green colour to the flame of alcohol.
Benzoate * .	Dilute solution of ferric sulphate	Flesh-coloured precipitate.
Bromide . .	Disulphide of carbon and chlorine water	If disulphide of carbon be poured into a solution of the salt, the chlorine water added drop by drop, and the whole agitated, the disulphide will acquire a yellow or yellowish-brown colour. (If iodine be present there will be a violet tint.)
Carbonate .	Acid . . .	Causes effervescence.
Bicarbonate .	,, . . .	Causes effervescence more abundant than in the case of the carbonate. With solution of mercuric chloride bicarbonates give a white, and carbonates a yellow precipitate.
Citrate * .	Calcium chloride .	The solution remains clear, but deposits white precipitate on boiling (calcium citrate being less soluble in hot than in cold water).
,, . .	Sulphuric acid and heat	Is charred and evolves the odour of acetic acid.
Chloride . .	Nitrate of silver .	White precipitate, soluble in ammonia, insoluble in hydrochloric or nitric acids.
Hypophosphite .	Heat . . .	Heated in a dry test-tube it evolves phosphoretted hydrogen, which takes fire spontaneously, and burns with a bright flame.
,, .	Nitrate of silver .	White precipitate, which rapidly turns brown and black.
,, .	Hydrochloric acid and mercuric chloride	White precipitate of calomel, and on further addition separation of metallic mercury.
Hyposulphite .	Sulphuric acid .	Gives rise to the smell of burning sulphur, and causes white precipitate of sulphur (bisulphite and sulphite give no precipitate).
Iodide . .	Disulphide of carbon and chlorine water	If disulphide of carbon be poured into a solution of the salt, then chlorine water added drop by drop, and the whole agitated, the disulphide of carbon will acquire a violet colour.
,, . .	Starch water, starch paste, or gelatinised starch, with chlorine water	Blue colour in the cold, discharged by boiling.
Nitrate . .	Sulphuric acid and copper	Nitrous fumes.
,, . .	Sulphuric acid and solution of ferrous sulphate	When sulphuric acid is added to a solution containing a nitrate, and a solution of ferrous sulphate is carefully poured over it, a dark colour appears at the junction of the two liquids.

Salt	Reagent	Reaction
Oxalate* . .	Calcium chloride .	White precipitate. In applying the test to cerium and iron, their salts must be decomposed by boiling with potash or soda. The oxide of cerium or iron is removed by filtration, and the reagent applied to the filtrate, which contains oxalate of potassium or sodium.
Phosphate .	Chloride of ammonium, ammonia, and sulphate of magnesium	White precipitate.
Phosphide .	Sulphuric or hydrochloric acid	Evolves phosphoretted hydrogen.
Salicylate * .	Ferric salts . .	Intense violet colour.
Sulpho-carbolate	Ferric chloride .	Violet colour. This salt can be distinguished from the salicylate by heat, when it gives off inflammable vapours having the odour of carbolic acid.
Sulphate .	Barium chloride .	White precipitate, almost insoluble in nitric acid.
Sulphide . .	Mineral acids, e.g. sulphuric or hydrochloric	Gives off sulphuretted hydrogen.
Sulphite . .	Ditto . .	Gives off sulphurous acid (has neutral or feebly alkaline reaction).
Bisulphite .	Ditto . .	Ditto (has acid reaction).
Tartrate*. .	Acetic acid in presence of potash	White crystalline precipitate of bitartrate.
,, . .	Sulphuric acid and heat	Is charred and evolves the odour of burnt sugar.
,, . .	Nitrate of silver .	White precipitate, becoming black on boiling.
Bitartrate * .	Nitrate of silver .	Solution rendered neutral by potash gives with the reagent a white precipitate becoming black on boiling (very sparingly soluble in water : is thus distinguished from neutral tartrate, which is readily soluble).
,, . .	Sulphuric acid and heat	Same reaction as tartrate.

* In the preceding table the salts of organic acids marked * when ignited in a crucible or on a piece of platinum foil, become charred and oxidised, leaving a residue which consists of carbonate. This is black from the presence of carbon, if ignition has not been carried sufficiently far to convert all the carbon into carbonic acid. This residue gives the reaction of a carbonate, effervescing with acids, and it is frequently convenient to convert the carbonate into chloride, before applying tests for the base.

Class I.—MONAD METALS.

Group I.—METALS OF THE ALKALIS.

Lithium, Sodium, Potassium, *Rubidium*, *Cæsium*.

Group II.—AMMONIUM.

I have omitted silver and gold from this class, because both their physiological actions and physical properties appear to show that they do not belong to it. I have put ammonium into a group by itself and separated it from the other members of this class, because it differs from them in being a compound and not an element; in being volatile; and in having an entirely different physiological action.

General Characters.—They are all powerful bases and have a great affinity for oxygen. The oxides of the first group are non-volatile, and are sometimes termed fixed alkalis, while ammonia is volatile. They all have a strong alkaline reaction, neutralising acids readily, turning red litmus-paper blue, and turmeric paper brown.

General Reactions.—They are not precipitated from solutions by the successive addition of (1) hydrochloric acid, (2) hydrogen sulphide, (3) ammonium sulphide, (4) ammonium carbonate, and (5) sodium phosphate.

General Physiological Action.—The alkalis are of great physiological importance, and salts of **potassium** and **sodium** form a large proportion of the saline constituents of the body. These two elements are differently distributed, potassium being chiefly found in solid tissues, while sodium is more abundant in the fluids. They are found as carbonates, bicarbonates, chlorides, phosphates, and sulphates. The proportion of these salts in the body is, however, very different, as are also their uses in the economy. The chlorides are by far the most abundant, and sodium chloride may be looked upon as the most important constituent of the nutritive fluids in which all the tissues of the body are bathed. But while sodium chloride forms the saline basis of these fluids, the other constituents are indispensable for the continued life of the tissues. All the fluids of the body are alkaline, and death occurs whenever the alkalinity is diminished below a certain point, even though the fluids and tissues are far from having an acid reaction. Such a reaction is only observed in the tissues after death. The importance of the different saline constituents in nutrition has been most fully worked out in the case of the frog's heart (p. 305 *et seq.*).

In the case of the **heavy metals**, which are not normal constituents of the body, the action of their **salts** depends almost

entirely on the base and only slightly on the acid with which it is combined. In the case of the alkalis, however, this is not so, the action of their salts depending much on the acid.

In consequence of this it is necessary in considering the physiological action of salts of the alkaline metals to divide them into at least three groups :—

1. Alkaline salts, hydrates, carbonates, and bicarbonates. (Sub-groups— Salts of organic acids, acetates, citrates, tartrates).
2. Chlorides.
3. Sulphates and other salts which are slowly absorbed.

General Action of the Alkaline Group.—Alkaline salts have their activity diminished by combination with carbonic or organic acids. The hydrates have an intense local action on the tissues; and the carbonates have an action, the same in kind, but much less in degree. In the case of the bicarbonates it is still further diminished, and in the acetates, citrates, and tartrates it is absent. The hydrates of potassium and sodium dissolve horny tissues such as the epidermis. They combine with albumen and form a soluble alkali-albuminate.

When applied to the skin the hydrated alkalis, which have a great affinity for water, withdraw it from the tissues and form a solution which softens and partly dissolves the epidermis and then acts on the softer textures below, combining with and dissolving them. Round the part thus killed inflammation sets in, and a slough separates. The rapidity with which they absorb water and form a solution which flows readily over adjacent parts, where its action is injurious, is an objection to their application, and the part actually cauterised by them should always be less than the part we wish to destroy. From this very property of widely destroying the tissues over which they flow, or through which they soak, they are admirably adapted for application in cases where we desire this effect, as in cauterising poisoned wounds.

When applied as caustics to unhealthy sores, cancer, &c., their action is sometimes limited by adding lime and forming the so-called Vienna paste (p. 346). The water which they withdraw from the tissues is sucked up by the lime, forming a solid hydrate and preventing the caustic from becoming too fluid and running over other parts. When less concentrated they may only irritate the surface sufficiently to produce exudation, but they generally soften or dissolve the epidermis so much that vesicles do not form well. When still more diluted they may cause only congestion or redness of the skin. They are then said to act as rubefacients. This rubefacient action may be used for the purpose of relieving troublesome itching in skin-diseases, or to produce derivation from other parts.

Ammonia does not dissolve the epidermis, and so, unlike potash or soda, it does not act as an immediate caustic, but only passes through the epidermis and irritates the skin below, causing lymph to be effused between it and the epidermis, and thus acting as a **vesicant**. It may, however, act as a caustic if its evaporation is prevented and it is applied too long, the irritation then becoming so great as to lead to suppuration, or even to sloughing of the part.

From their great solvent power, and especially their power of dissolving greasy substances, alkalis are used for **cleansing** the skin, but when used alone they very frequently produce irritation, and we therefore generally employ them in the form of soap, or in the form of those salts which have only a very slight alkaline character, such as borax.

In the **mouth** they neutralise any acid present They may thus relieve toothache due to irritation of the exposed nerve in a carious tooth or of the roots of the teeth close to the gums by acid secretions. A dilute solution of sodium bi-carbonate as a wash to the mouth frequently relieves soreness of the teeth, or headache depending on dental irritation, and prevents injury from acid tonics. Alkalis are used in the shape of borax to heal aphthæ in the mouth and as soap for cleaning the teeth.

In the **stomach** they increase the amount of gastric juice secreted; and where this is deficient and the food lies heavy and is digested slowly and with difficulty, they should be given before a meal or just at its commencement, either in the form of a medicinal mixture or as aërated potash or soda water. The amount of acid secreted by the stomach after their introduction is sufficient to neutralise them pretty rapidly, and probably only the caustic alkalies which act very rapidly have time to produce any local action before they are neutralised, unless large quantities have been ingested. Where there is a large amount of mucus on the surface of the stomach it will both hinder the exit of the gastric juice from the follicles and the entrance of the peptones from the stomach into the blood. Caustic alkalies have a great power of dissolving mucus. They probably do this to some extent before they are neutralised, and this may be the reason why we occasionally find that they are of great service when a corresponding amount of their carbonates does little or no good. From the effect they produce on the secretion of gastric juice, alkalis in small doses are said to act as **gastric stimulants** (p. 363).

When the amount of acid in the stomach is too great, either because too great a proportion of it has been present in the gastric juice, or because it has been generated by the decomposition of food, digestion goes on slowly, and burning acid eructations take place after meals. In such cases we give alkalis to neutralise the excess and to restore the proportion of acid in the stomach to its normal. They are then said to act as **antacids** (p. 369).

Alkalis are serviceable as **antidotes** in poisoning by acids, metals, and alkaloids. They neutralise the acids, they precipitate the metals as insoluble oxides, and they render alkaloids less soluble by taking away the acid with which they are generally combined. They thus retard their absorption and afford time for the use of other means.

The chyme from the stomach is normally acid, and will therefore act as a stimulus to the expulsion of bile from the gall-bladder. It is partly neutralised by the bile and pancreatic juice, but generally remains acid throughout the small **intestines** and will act as a stimulus to the secretion of intestinal juice. If it be neutralised by alkalis in the stomach, this stimulus will be removed and digestion consequently impaired. Many substances will thus pass through the intestinal canal undigested, which amounts to the same thing as if less food had been taken.

Through this derangement of the digestion the blood will become poorer in solids, the person will become emaciated, the fat will naturally be first absorbed, and, along with this, perhaps pathological formations may also disappear.

The excessive use of alkalis or their carbonates is thus injurious, and their employment to reduce obesity may, unless carefully watched, be followed by serious consequences, like the use of acids for a similar purpose (p. 569).

Caustic alkalis injected directly into the blood cause death in a few minutes, probably from formation of alkali-albuminate in the blood and its consequent coagulation. Shortly after death the blood is found coagulated. Smaller amounts taken in from the stomach will to some extent increase the alkalinity of the blood, but are rapidly separated by the **kidneys.** They cause thirst, and probably the larger amount of water drunk in consequence is one cause of the diuresis they produce. From their power of dissolving fibrin outside the body, they have been given in acute rheumatism to prevent fibrinous deposits on the heart. It is not certain that the amount we can introduce into the blood without injury to the patient has this effect.

After small doses of liquor potassæ the urea and sulphuric acid in the urine are increased, and Parkes therefore thinks that the tissue-change of the albuminous substances is increased. Alkalis are therefore classed as **alteratives** (p. 414).

They are used both to increase the amount of water passed and to diminish its acidity if this be excessive. They are therefore classed amongst **diuretics** (p. 432), and **remote antacids** (p. 370).

General Action of the Group of Chlorides.—Chloride of sodium is not only one of the most abundant saline constituents of the animal body, but it is one of the most important **solvents** of albuminous substances. Water will dissolve albumins proper, but globulins are insoluble in it, and are precipitated by it from

solutions. Dilute solutions of chloride of sodium on the contrary dissolve both albumins and globulins. From this action of water on albuminous substances it is very irritating when applied to a cut surface, or to the delicate mucous membrane of the nose, while muscles dipped in it swell up, and pass into a state of rigor. Weak solutions of chloride of sodium, on the other hand, have no irritating action, and may be applied to cut surfaces or mucous membranes without causing pain, and to muscle and nerve without producing any injurious effect. A solution of the strength of 0·65 per cent. is the one usually employed in physiological experiments as a basis for the nutritive fluid in artificial circulation through the frog's heart or vessels, and as a solvent for alkaloids which are to be injected into the lymph-sac of the frog, in order to avoid the local irritation which the injection of a watery solution would produce. A solution of this strength is often called 'normal salt solution' in physiological treatises.

While dilute solutions of chloride of sodium are ready solvents of albuminous substances and are non-irritating, sodium chloride, in substance or in concentrated solutions, precipitates globulins, withdraws water from the tissues, and acts as an exceedingly powerful irritant to cut surfaces, mucous membranes, muscle, and nerve. Common salt taken in a large quantity at once will irritate the **stomach** and cause vomiting. It is **absorbed** with great rapidity, but it is also excreted so rapidly that it produces no definite symptoms of irritation in any part of the body, excepting that part of the **nervous system** by which the sensation of thirst is perceived. This sensation becomes so urgent when much salt has been taken that any risk will be encountered in order to gratify it. Should it be impossible to obtain fresh water, other parts of the nervous system become involved, and travellers whose supply of water has failed in the desert, or shipwrecked sailors who have drunk sea-water, have become delirious. It is difficult to say, however, how far the delirium is due to the direct irritant action of sodium chloride on the brain, as many other factors may concur in its production. Under ordinary circumstances, the thirst occasioned by sodium chloride after its absorption, causes as much water to be drunk as will allow the salt to be excreted by the **kidneys**, leaving the proportion both of salt and water in the body nearly the same as before. During its stay in the body the salt does not appear to alter the composition of the **tissues**, and the chief alterations produced by it are probably due to its action on the solubility of albuminous substances and on the processes of osmosis between the intercellular fluid and blood, and the circulation of lymph in the tissues. In consequence of this, sodium chloride increases tissue-change, as is shown by an increase in the amount of urea excreted. A similar increase, however, occurs when the quantity usually taken is diminished, the amount of water daily consumed

remaining the same. The alteration here is probably also due to increased rapidity of the circulation of fluid through the tissues (Voit), but it may also be due in part to the different solubilities of albuminous substances in solutions of sodium chloride of different strengths. Certain albuminous tissues may thus be affected by one proportion of salt in the blood, others by another, so that increase and diminution of the normal proportion of sodium chloride may increase tissue-change in the body as a whole, though not in the same tissues. The **proportion** of chloride of sodium in the body is not always the same. It depends on the quantity taken daily, and may be increased or diminished within certain limits. If a definite quantity be taken daily for some time, the same quantity will be found in the urine, so that the amount present in the body is constant. If the quantity consumed be now increased, no increase takes place in the excretion for about three days, a **storage** of salt taking place in the body. After about three days the quantity excreted daily in the urine will again be found equal to the quantity daily taken, the amount present in the body remaining constantly at the higher level. If the quantity daily taken be now diminished, no diminution takes place in the quantity excreted for about three days, and then the quantities daily taken and excreted again correspond. The amount stored up at first is now gone, and the proportion of salt in the body is now again reduced to its lower level.[1]

Increased consumption of sodium chloride not only increases the quantity of it and of urea in the urine but increases also the **excretion** of **potassium** salts.

On the other hand, potassium salts also increase the excretion of sodium. Between salts containing no chlorine, such as carbonate or phosphate, and the sodium chloride in the blood, a double decomposition takes place, potassium chloride, and sodium carbonate or phosphate, being formed. These newly-formed salts are unnecessary for the organism, and are excreted in the urine along with the unaltered remainder of the phosphate or carbonate administered. Considerable quantities both of chlorine and sodium may thus be removed from the organism. In consequence of this, herbivorous animals and people living chiefly on a vegetable diet, and who thus consume considerable quantities of potassium salts, feel the need of sodium chloride greatly, and on the American prairies the herds of buffaloes travel hundreds of miles to visit the salt licks. Beyond a certain point, however, the excretion of sodium chloride is not increased by potassium salts, and when the quantity of sodium salts in the body is low, excretion is not increased at all.

When an abnormal quantity of fluid is present in the tissues,

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[1] Ludwig, *Manuscript Notes of Lectures*, 1869–1870.

as in dropsies, an increase in the saline constituents of the blood may cause its absorption, especially if the quantity of water drunk by the patient be limited. It is probable that in addition to their diuretic action the alkaline salts affect the nutrition of the tissues themselves, and that salts of potassium are better than those of sodium in cases of dropsy, because of their action on the tissues.

GENERAL ACTION OF THE SUB-GROUP OF SULPHATES, &c.—This group contains salts which are sparingly absorbed, such as sulphates, phosphates, and bitartrates. That they are sparingly absorbed is shown by the fact that when administered internally they only appear to a small extent in the urine. They usually act as **purgatives**, but if from any cause their purgative action should be prevented, and they remain long in the intestine, absorption will occur, though slowly. In herbivorous animals, which have a much longer intestinal canal than carnivora, larger doses of these salts are required to produce a purgative action. The mode of action has already been discussed (p. 390 *et seq.*).

COMPARATIVE ACTION OF THE ALKALINE METALS.—As the action of the base appears to be less modified by the acid radical in the case of the chlorides than of other salts of the alkaline metals, they are better adapted for experiments on the comparative action of the members of this class.

Group I.—The chlorides of lithium, sodium, potassium, rubidium, and cæsium produce in **frogs** gradually increasing torpor, paralysis, and death. The chief action appears to be on the **spinal cord**, which is **paralysed,** a slight primary excitement occurring in the case of potassium and rubidium. Lithium and potassium paralyse also the ends of the **motor nerves.** Sodium does so also, though to a much less extent. Cæsium and rubidium do not do so, excepting when given in very large doses.

The contractile power of **muscle** is almost always diminished by lithium, unaffected by sodium, and increased by the other members of this group in small or moderate doses. Large quantities of potassium diminish both the irritability and contractile power of muscle voluntary and involuntary.

In frogs the **heart** becomes weaker and finally stops in diastole.

Group II.—Ammonium differs entirely from the members of the first group in the symptoms it produces. While they paralyse the spinal cord with little or no previous excitement, causing torpor and death, ammonia at first **stimulates** the cord, producing tetanic convulsions. The action of ammonium is considerably modified by the acid radical with which it is combined. All the ammonium salts have an action on the **spinal cord, motor nerves,** and **muscles,** and, in advanced poisoning, **paralyse** these structures.

They do not, however, affect all these structures with equal

readiness. The organ first affected, and consequently (p. 26) the symptoms of poisoning, vary with the salt employed. Some salts affect the spinal cord first, others the motor nerves. Ammonia and ammonium chloride produce tetanus. The bromide produces hyperæsthesia with some clonic spasm, passing into tetanus, which, however, comes on very late.

The sulphate also produces hyperæsthesia and clonic spasms, but rarely tetanus. The phosphate produces paralysis without convulsions, either clonic or tonic, the only indication of any convulsant action being slight twitches accompanying movements in the hind limbs before reflex action has ceased. The iodide produces progressive paralysis and no tetanus. The brain appears to be affected before the spinal cord. This is shown by the frog croaking when stroked, as it does after removal of the cerebral hemispheres, and by the reflex from the conjunctiva failing before that from the limbs.

Ammonium salts appear to form a **series**, at one end of which the members **stimulate** the spinal **cord** and have no marked paralysing action on the motor nerves, while those at the other end have no marked stimulating action on the cord, but, on the contrary, have a marked **paralysing** action both on the **cord** and on **motor nerves.** At the stimulating end of this series are ammonia and ammonium chloride, and at the paralysing end ammonium iodide; whilst the bromide, phosphate, and sulphate lie between.

Group I.—METALS OF THE ALKALIS.

POTASSIUM. K; 39.

General Sources of Potassium Salts.—The chief source of potassium salts is the ash left by the combustion of plants or trees; but there are two subsidiary sources, viz. nitrate of potassium, which is found native, and bitartrate of potassium, which is deposited from wine in the process of fermentation.

General Reactions of Potassium Salts.—In analysis, potassium is distinguished from all other bases, excepting magnesium, sodium, and ammonium, by not being precipitated by ammonium sulphide nor carbonate of ammonium. The positive reactions by which its presence is ascertained are—(1) its precipitation when converted into an acid tartrate; (2) its precipitation by perchloride of platinum; (3) the violet colour it imparts to flame.

The sparing solubility of the **acid tartrate** is the test which is used in the U.S.P. to distinguish all salts of potassium. The reagent employed is tartaric acid in the case of potassium hydrate, carbonate, and bicarbonate; in the case of the tartrate of potassium and sodium, acetic acid is used. In the case of

most other salts a saturated solution of bitartrate of sodium is added to their aqueous solution. Potassium chlorate is calcined and the reagent added to a solution of the residue. Potassa sulphurata is decomposed by boiling with hydrochloric acid, the sulphur removed by filtration, and the filtrate neutralised by soda before the reagent is applied. No test for potassium is given in the case of potassium bitartrate or permanganate.

This test is only employed in the British Pharmacopœia in four instances—viz. neutral tartrate, acetate, bromide, and iodide. In the case of the neutral tartrate the test is applied by adding a small quantity of acetic acid, and thus producing acid tartrate. In the case of the acetate, bromide, and iodide, it is applied by adding tartaric acid. On the addition of **perchloride of platinum** to chloride of potassium a double chloride of potassium and platinum is formed, and falls as a sparingly soluble pale-yellow precipitate. If the potassium salt be other than a chloride, part of the chlorine in the platinum salt is used up to convert the potassium into a chloride, and thus loss of the expensive reagent takes place. To avoid this loss hydrochloric acid is always to be added before the addition of the platinum salt. This reaction is not used for the bromides and iodides, because bromide and iodide of platinum would be formed and a loss of the reagent would occur. In testing some potassium salts, **modifications** are observed in the mode of applying the test. Before applying it to the chlorate the salt is calcined, oxygen is thus driven off, and the residue, consisting of chloride of potassium, does not require the addition of hydrochloric acid. The permanganate is also calcined, but the potash contained in the residue, after being dissolved out by water from its admixture with manganese dioxide requires to be treated with acid as usual. In the case of the sulphide the hydrochloric acid causes the evolution of hydrogen sulphide, which must be removed by boiling, and causes also the precipitation of sulphur, which must be removed by filtration before the addition of platinum chloride.

PREPARATION OF POTASSIUM SALTS.

	Prepared from	By
Potassium carbonate, B. and U.S.P.	Wood ashes . .	Lixiviating, evaporating, and crystallising.
Liquor potassæ, B.P. „ potassii, U.S.P.	Potassium carbonate	Treating solution with slaked lime and partially evaporating.
Caustic potash, B. and U.S.P.	Do. .	Ditto, and evaporating to dryness.
Potassium bicarbonate, B. and U.S.P.	Do. .	Passing carbonic acid gas into solution.
Potassium sulphite, U.S.P.	Do. .	Passing sulphurous acid gas into strong solution until acid, adding equal weight of potassium carbonate and crystallising.

PREPARATION OF POTASSIUM SALTS—(*continued*).

	Prepared from	By
Potassium acetate, B. and U.S.P.	Potassium carbonate	Dissolving in acetic acid.
Potassium citrate, B. and U.S.P.	Do. .	Neutralising with citric acid.
Potassium hypophosphite, U.S.P.	Do. .	Decomposing by hypophosphite of calcium.
Potassium chlorate, B. and U.S.P.	Do. .	Treating with lime and chlorine.
Potassa sulphurata, B. and U.S.P.	Potassium carbonate and sulphur	Heating together.
Potassium ferrocyanide, B. and U.S.P.	Potassium carbonate	Fusing with animal matter and iron; lixiviating and crystallising.
Potassium cyanide, B. and U.S.P.	Potassium ferrocyanide	Igniting either alone, or with carbonate of potassium. The former process is official B.P. and gives a purer, the latter a more abundant product.
Potassium acid tartrate, B. and U.S.P.	Crude tartar or argol	Treating with charcoal or clay.
Potassium tartrate, B. and U.S.P.	Acid tartrate of potassium	Neutralising with potassium carbonate.
Potassium nitrate, B. and U.S.P.	Native . . .	—
Potassium sulphate, B. and U.S.P.	Acid sulphate left from admixture of sulphuric acid and potassium nitrate in the preparation of nitric acid	Neutralising with carbonate of potassium or calcium.
Potassium permanganate, B. and U.S.P.	Chlorate of potassium, caustic potash, and oxide of manganese	Ignition together, boiling and neutralising.
Potassium bichromate, B. and U.S.P.	Chromate of potassium	Treating with sulphuric acid.
Potassium iodide, B. and U.S.P.	Potash and iodine .	Mixing and heating with charcoal.
Potassium bromide, B. and U.S.P.	Potash and bromine.	As in the iodide.

GENERAL ACTION OF POTASSIUM SALTS.—According to Ringer, potassium is a **protoplasmic poison** destroying muscle, nerves, and nerve-centres when applied to them sufficiently long and in a sufficiently concentrated form. But this action is not peculiar to potassium, for sodium, ammonium, hydrocyanic acid, and probably many other substances possess it. Potassium salts differ from sodium salts in **diffusing** more readily through membranes. They are more easily absorbed and more easily excreted than sodium salts. In the living organism they **occur** chiefly in the solid structures, such as blood-corpuscles and muscles, while sodium salts occur chiefly in the fluids of the body.

When applied to **muscle**, potassium salts in minute doses may increase its contractile power (p. 135); but in larger doses, or when

continued for a longer time, they diminish its power and finally paralyse it altogether. They remove the excessive prolongation of muscular contraction produced by veratrine, barium, calcium, strontium, and by large doses of sodium or lithium (p. 135).

They have a somewhat paralysing action on **motor nerves.** They paralyse also the **nerve-centres,** generally after a primary, transitory, excitement.

A peculiar difference in the action of sodium and potassium salts locally applied to the intestine has been already noticed (p. 383). Large doses paralyse the muscular fibre of the intestines, and it is possible that this paralysing action is the cause of the digestive disturbances which the prolonged use of potassium salts causes (Rossbach).

When administered by the mouth they may produce, like other salts in large doses, irritation of the **gastro-intestinal** canal. They are, however, so quickly **excreted** that they can hardly produce poisoning by their action on the heart while circulating in the blood; they probably modify the nutrition of the tissues and act as alteratives. It is probable that potassium salts may accumulate to a certain extent in the body in the same way as sodium chloride (p. 601). By feeding animals with potassium salts the poisonous action of barium may be lessened. Cash and I have now found that when injected simultaneously with salts of barium (cf. p. 137), they will antagonise the action of the latter, and prevent death from an otherwise lethal dose of barium. Similar experiments with potassium and veratrine have given negative results. The prolonged use of potassium salts is apt to cause some depression, and larger doses continued for some time may diminish the force of the circulation. They do not paralyse the **heart** when given by the mouth, but when injected directly into the veins they produce transitory excitement, clonic spasms, paralysis, and death.

Death is preceded by convulsions, and is caused by stoppage of the heart while respiration still continues. Even after both heart and respiration have ceased and the animal is apparently dead, life may be restored by the patient use of artificial respiration, and mechanical irritation of the heart by compressing the cardiac region. After the heart has thus been induced to beat spontaneously, respiration still remains in abeyance for some time. The **nerve-centres** are also paralysed, and neither voluntary movement nor reflex action occur for some time. When **reflex excitability** returns it is often much exaggerated, so that a slight shake or gentle touch on the surface may cause spasms. In this respect potassium somewhat resembles atropine, and the possible explanation of this action has already been discussed (p. 171 *et seq.*).

The effect of potassium salts on the **circulation** somewhat resembles that of digitalis. In large doses they cause a rapid fall of the blood-pressure and pulse-rate. Smaller doses cause a

slight fall of both pulse-rate and pressure, followed by a rise of both. During the rise of pressure, however, the pulse becomes again slow, and continues so even when the pressure again begins to fall to the normal. The rise of pressure occurs even when the spinal cord is divided, and probably depends on contraction of the arterioles (p. 281).

Potassii Carbonas, B. and U.S.P. CARBONATE OF POTASSIUM, K_2CO_3, with about 16 per cent. of water of crystallisation, B.P. $(K_2CO_3)\ 3H_2O$; 330, U.S.P.

CHARACTERS.—A white crystalline powder, alkaline, and caustic to the taste, very deliquescent.

SOLUBILITY.—It is readily soluble in water, but insoluble in spirit.

REACTION.—It gives the reactions of a carbonate (p. 594) and of potassium (p. 603).

20 grains Carbonate of Potassium } neutralise { 17 grains Citric Acid, or 18 grains Tartaric Acid.

DOSE.—10 to 30 grains.

ACTION.—When taken internally it acts as an **irritant** poison. It is rarely used internally, but may be given instead of liquor potassæ, or of bicarbonate, or in an effervescent form with citric or tartaric acid. It is chiefly employed in the preparation of other potassium salts. A dilute solution of it may be used as an application to the skin to relieve itching, and for this purpose may be alternated with dilute acid. Carbonate of potassium is also used as an ingredient in sulphur ointments (Ung. Sulph. Alk. U.S.P. p. 544) in cases of indurated acne: the strength may be half a drachm to a drachm in the ounce of ointment.

Liquor Potassæ, B. and U.S.P. SOLUTION OF POTASH, B.P.; OF POTASSA, U.S.P.—An aqueous solution of hydrate of potassium (KHO; 56) containing 5·84 per cent. of the hydrate, B.P.; about 5 per cent., U.S.P.

DOSE.—15 to 60 minims.

USES.—Dilute liquor potassæ is used **externally** as a lotion in freckles, and when diluted with water in the proportion of 1 to 6, is employed in order to soften ingrowing toe-nails. **Internally** it acts both as a direct and remote **antacid** and as an **alterative**. It is given in scaly skin-diseases, in eczema and acne, especially when these occur in gouty subjects, or are accompanied by acidity of the stomach. In cases of dyspepsia, with irritability, it is said to have a **sedative** action upon the stomach, and thus to be preferable to the bicarbonate. It is believed to be useful in jaundice, and in enlargement or cancer of the liver. For its action upon the system it has been administered in rheumatism, both acute and chronic. It is given to cause the **absorption** of fat in obese persons, but may destroy the general health (cf. p. 599). It has been used to cause the

absorption of scrofulous glands and of bronchocele. It increases the bronchial secretion, and renders it more liquid and easier to cough up. It is therefore useful in bronchitis where the secretion is scanty and difficult to expectorate, and is equally serviceable in the intercurrent bronchitic attacks to which phthisical patients are liable (p. 252).

Potassa Caustica, B.P.; Potassa, U.S.P. KHO; 56. CAUSTIC POTASH.—Hydrate of potassium, KHO, containing some impurities.

CHARACTERS.—In hard white pencils, very deliquescent, powerfully alkaline and corrosive.

REACTIONS AND TESTS.—A watery solution gives the reactions of potassium (p. 603) and those showing the absence of impurities.

PREPARATION CONTAINING CAUSTIC POTASH.

Liquor Potassæ..............27 grains in 1 fluid ounce.

PREPARATION IN WHICH CAUSTIC POTASH IS USED.

Potassii Permanganas.

USES.—It is used as a **caustic** where we wish to burn deeply and widely, as in snake-bites, the bites of rabid animals, or in poisoned wounds. It is occasionally employed to open abscesses, more especially abscess of the liver, in which it is sometimes preferred to the knife, as by its use we secure adhesion of the liver to the abdominal wall before the abscess is opened, and thus prevent any pus from finding its way into the peritoneal cavity. Ringer says that the best way to apply it is to cut a hole in a thick piece of plaster, smaller than the size of the slough which we wish to make, and rub on the caustic potash, slightly wetted until the tissues assume a greyish colour, then to wash the part with vinegar, and apply a poultice. Solutions of caustic potash of the strength of 10 to 30 grains to the ounce of distilled water are useful in dissolving the thickened patches of old eczema: acetic acid must be applied to neutralise the potash, and the treatment renewed once or twice a week.

U.S.P. Potassa cum Calce. Potassa with Lime; Vienna Paste.

CHARACTERS.—It is a greyish-white, deliquescent powder with a strongly alkaline reaction.

REACTION.—It gives the tests of potassium (p. 603) and calcium (p. 646).

PREPARATION.—Equal parts of caustic potash and lime made into a paste with alcohol.

USES.—It is used for the same purposes and in the same manner as caustic potash, but being less deliquescent its action is slower and more limited; it is thus more easily restricted to the part which it is wished to destroy, and is less liable to spread.

Potassii Bicarbonas, B. and U.S.P. BICARBONATE OF POTASSIUM. $KHCO_3$; 100.

CHARACTERS.—Colourless right rhombic prisms, not deliquescent, of a saline feebly alkaline taste, not corrosive.

REACTIONS AND TESTS.—It gives the reactions of a bicarbonate (p. 594 and of potassium (p. 603) and those showing the absence of impurities.

20 grains Bicarbonate of Potassium } neutralise { 14 grains Citric Acid, or 15 grains Tartaric Acid.

DOSE.—10 to 40 grains.

PREPARATION.

B.P.

Liquor Potassæ Effervescens (Potash water)............30 grs. in 1 pint.

USES.—Solutions of bicarbonate of potassium may be used **externally** to relieve itching. **Internally** it is given in dyspepsia, rheumatism, gout, and scalding depending upon excessive acidity of the urine with presence of uric acid, or in cases of deposit of this acid in the urinary passages.

Potassii Acetas, B. and U.S.P. ACETATE OF POTASSIUM $CH_2K(CO{\cdot}OH)$; 98.

CHARACTERS.—White foliaceous satiny masses, very deliquescent.

REACTIONS.—With a watery solution, tartaric acid causes a crystalline precipitate (potassium), sulphuric acid the disengagement of acetic acid, and a dilute solution of perchloride of iron strikes a deep red colour (acetate).

IMPURITIES.—Acid, carbonate, lead.

TESTS.—Neutral to test paper (no acid); almost entirely soluble in rectified spirit (no carbonate). Its solution is unaffected by sulphide of ammonium (no metals).

DOSE.—10 to 60 grains.

PREPARATION IN WHICH ACETATE OF POTASSIUM IS USED.

Tinctura Ferri Acetatis.

USES.—From its slight local action and its great solubility it produces little effect directly on the stomach and is easily absorbed into the blood. Here it is converted into carbonate and renders the blood and the secretions which come from it more **alkaline**. This salt of potassium is one which is very frequently used for the purpose of rendering the urine alkaline. It is one of the most powerful saline **diuretics** we possess, and is much used in dropsies, alone or combined with other diuretics, or with tonics and stimulants, e.g. acetate of iron and acetic ether.

When given in large doses (120 grains and upwards) and in a concentrated form it acts as a **purgative**.

It is employed, like other potassium salts, as an **alterative** in acute rheumatism, skin diseases, and enlarged glands.

Potassii Citras, B. and U.S.P. CITRATE OF POTASSIUM. $K_3C_6H_5O_7$. B.P. $K_3C_6H_5O_7.H_2O$; 324. U.S.P. LIQUOR POTASSII CITRATIS, U.S.P.

CHARACTERS.—A white powder, of saline feebly acid taste, deliquescent, and very soluble in water.

REACTIONS AND TESTS.—Heated with sulphuric acid it forms a brown fluid, gives off an inflammable gas and evolves the odour of acetic acid (citrate). Its solution gives the reactions of potassium (p. 603) and, mixed with a solution of chloride of calcium, remains clear till it is boiled, when a white precipitate separates which is readily soluble in acetic acid. This precipitate is citrate of calcium, which is less soluble in hot than in cold water.

DOSE.—20 to 60 grains.

USES.—Is very pleasant to the taste, produces no local action and is very soluble. It is thus easily absorbed into the blood, and there becomes carbonate. It is less liable to purge than other potassium salts, and can thus be given in larger doses. After absorption it acts like the carbonate, causes **diuresis** and **lessened acidity** or even alkalinity of the urine, and probably influences tissue-change as well. It is **antiscorbutic.**

Potassii Tartras Acida, B.P.; Potassii Bitartras, U.S.P.
ACID TARTRATE OF POTASSIUM, B.P.; BITARTRATE OF POTASSIUM, U.S.P. CREAM OF TARTAR. $KHC_4H_4O_6$; 188.

An acid salt obtained from the crude tartar which is deposited during the fermentation of grape-juice, B.P.

CHARACTERS.—A gritty white powder, or fragments of cakes crystallised on one surface; of a pleasant acid taste.

SOLUBILITY.—Sparingly soluble in water, insoluble in spirit.

REACTIONS AND TESTS.—Heated in a crucible it evolves inflammable gas and the odour of burnt sugar, and leaves a black residue (tartrate). The calcined residue consists of potassium carbonate and gives its reactions.

DOSE.—20 to 60 grains as a diuretic; $\frac{1}{4}$–$\frac{1}{2}$ oz. as purgative.

PREPARATIONS IN WHICH ACID TARTRATE OF POTASSIUM IS USED.

B.P.	U.S.P.
Acidum Tartaricum.	Pulvis Jalapæ Compositus.
Antimonium Tartaratum.	
Confectio Sulphuris.	
Ferrum Tartaratum.	
Potassii Tartras.	
Pulvis Jalapæ Compositus.	
Soda Tartarata.	

USES.—From there being two equivalents of tartaric acid to one of potassium it has a somewhat acid taste, and is used instead of tartaric or other acids for making **cooling** drinks in fevers, &c. A refreshing drink called Potus Imperialis, or Imperial, is made by dissolving 1 to $1\frac{1}{2}$ drachm of acid tartrate and a little sugar in a pint of boiling water and infusing with half the fresh peel of a lemon.

In small doses it is absorbed, oxidised in the blood to carbonate, and acts like the acetate as a **diuretic.**

In larger doses it retains water with great avidity, and pre-

vents its absorption into the blood for a long time. It therefore causes the stools to be very watery, by detaining water in the intestine, but it has no irritating action on the intestine, and produces no increased peristalsis. If no other medicine be given to cause peristalsis, the salt and the water it has been retaining will be absorbed. Its action is thus very much like that of a simple enema of water going along the whole intestine, and like a simple enema it produces no depressing effect.

It is much used in dropsies as a **purgative**, generally in combination with jalap or scammony to produce peristalsis, whether the dropsy be due to affections of the heart or kidneys, and also in Bright's disease, even when unaccompanied by dropsy. It has also been employed as a laxative in dysentery, piles, and prolapsus ani.

Potassii Tartras, B. and U.S.P. TARTRATE OF POTASSIUM, $K_2C_4H_4O_6.H_2O$ (B.P.), or $(K_2C_4H_4O_6)_2H_2O$; 470 (U.S.P.).

CHARACTERS.—In small, colourless, four or six-sided prisms.

REACTIONS.—It gives the reactions showing the presence of tartaric acid and potassium like the bitartrate, but it is readily distinguishable by its greater solubility in water.

IMPURITY.—Bitartrate.

TEST.—Entirely dissolved by its own weight of water.

DOSE.—As a diuretic, 20–60 grains. As a purgative, $\frac{1}{4}$–$\frac{1}{2}$ ounce.

USES.—In small doses it is absorbed, converted into carbonate in the blood and acts as a **diuretic, antilithic**, &c., like the acetate and citrate. In larger doses it acts as a **purgative**, like other saline cathartics.

Potassii Sulphas, B. and U.S.P. SULPHATE OF POTASSIUM. K_2SO_4; 174.

CHARACTERS.—Colourless hard six-sided prisms terminated by six-sided pyramids.

SOLUBILITY.—Sparingly soluble in water, insoluble in alcohol.

REACTIONS.—It decrepitates strongly when heated. Its solution in water gives the reactions showing the presence of potassium and a sulphate (*v.* p. 595).

IMPURITIES.—Calcium, chlorides, iron and lead.

TEST.—The solution should give no precipitate with oxalate of ammonium (no calcium), nitrate of silver (no chloride), nor ammonium sulphide (no metals).

DOSE.—15 to 60 grains.

PREPARATIONS.

B.P.

Pilula Colocynthidis Composita (p. 522)	1 part in	24.
„ „ **et Hyoscyami** (p. 522)	1 „	36.
„ **Ipecacuanhæ cum Scilla** (p. 522)	1 „	3.
Pulvis Ipecacuanhæ Compositus	4 „	5.

USES.—Sulphate of potassium is employed as a saline **purgative** in cases of dyspepsia, biliousness, and albuminuria. It is generally combined with some other aperient, such as rhubarb. From its hardness it is used to aid in pulverising tough vegetable substances, like ipecacuanha in the preparation of Pulv. Ipecacuanhæ Co., B.P. It was once supposed to have the power of arresting the secretion of milk, and was therefore given to women who wished to stop suckling.

Potassii Nitras, B. and U.S.P. NITRATE OF POTASSIUM. KNO_3; 101.

Nitrate of potassium of commerce, purified, if necessary, by crystallisation from solution in distilled water.

CHARACTERS.—In white crystalline masses or fragments of striated six-sided prisms, colourless, of a peculiar cool saline taste.

REACTIONS.—Thrown on the fire it deflagrates; warmed in a test-tube with sulphuric acid and copper wire it evolves ruddy fumes (nitrate). Its solution gives the reactions of potassium (p. 603).

IMPURITIES.—Sulphates and chlorides, which are detected by the usual tests (*v.* p. 594).

DOSE.—10 to 30 grains.

PREPARATIONS.

B.P. Argenti et Potassii Nitras. U.S.P. Argenti Nitras Dilutus.

U.S.P. Charta Potassii Nitratis. Nitrate of Potassium Paper. Unsized paper dipped in a 20 per cent. solution of nitrate of potassium and dried.

ACTION.—In large doses, nitrate of potassium will produce death by **gastro-enteritis**, with vomiting, weakness, and arrest of the circulation, due partly to the reflex action of the drug, and partly to its direct action on the **heart** after absorption. When injected into the blood, it slows the pulse by lessening the irritability of the cardiac ganglia, lowers the **temperature**, and causes dyspnœa and death with convulsions. The convulsions are due to arrest of the heart, and consequent irritation of the brain by venous blood.

USES.—Nitrate of potassium gives up its oxygen readily, and paper dipped in a strong solution of it (Charta potassii nitratis, U.S.P.) and then dried, may be burnt in a plate, and the fumes inhaled, in asthma. It has been suggested that among the products of combustion the nitrite of potassium is the most efficacious. A ball of nitre, kept in the mouth and allowed to melt slowly away, gives relief in cases of relaxed sore-throat. It has been used internally in acute bronchitis, spasmodic asthma (either internally or by inhaling its fumes), and in dyspepsia with congestion of the mucous membranes. Generally it is avoided in inflammation of the stomach, intestine, kidneys, and bladder, on account of its local irritant action. On account of its action on the heart it has been given in hæmoptysis and other hæmor-

rhages. On account of its supposed action on the blood it was, and is, used in inflammation, fevers, and exanthemata. As an alterative it is used in scurvy, purpura, rheumatism, and gout. Twenty grains of nitre with thirty of potassium bicarbonate taken in the morning in a large soda-water tumbler full of water will sometimes prevent the onset of a gouty paroxysm, and will also remove the headache consequent upon a debauch. Nitrate of potassium is also used as a **diuretic** in cases of dropsy and gonorrhœa, and as a stimulant to the bladder in cases of incontinence of urine.

Potassii Chloras, B. and U.S.P. CHLORATE OF POTASSIUM, $KClO_3$; 122·4.

CHARACTERS.—In colourless rhomboidal crystalline plates, with a cool saline taste.

PREPARATION.—By passing chlorine through a mixture of potassium carbonate and slaked lime. If potassium carbonate alone were used part of it would be converted into KCl and lost. $3K_2CO_3 + 3Cl_2 = 5KCl + KClO_3 + 3CO_2$. To save this, lime is used, which is much cheaper. After the mixture has been saturated with chlorine it is boiled, filtered, evaporated, and the chlorate crystallised out. $K_2CO_3 + 6CaH_2O_2 + 6Cl_2 = 2KClO_3 + 5CaCl_2 + CaCO_3 + 6H_2O$.

SOLUBILITY AND REACTIONS.—Sparingly soluble in cold water. It explodes when triturated with sulphur. When heated it fuses, gives off oxygen gas, and leaves a white residue, which dissolves in water and gives the reactions of potassium and of a chloride.

IMPURITIES.—Chloride and calcium.

TEST.—Its solution is not affected by nitrate of silver (no chloride) nor oxalate of ammonium (no calcium).

DOSE.—10 to 30 grains.

OFFICINAL PREPARATIONS.

B.P. and U.S.P.	DOSE.
Trochisci Potassii Chloratis.........	5 grains in each lozenge.—1 to 6.

Used also in preparing Potassii Permanganas.

ACTION.—Chlorate of potassium, when injected into the circulation, has not the same action as other salts of potassium. Small doses generally at first depress, and afterwards raise the **blood-pressure** and accelerate the **pulse**. Large doses cause sudden stoppage of respiration, and sinking of the blood-pressure down to zero, while the exposed heart continues to beat at nearly its normal rate, or a little over it, for half or three-quarters of an hour.

Large doses administered medicinally have caused poisoning, especially in children. The symptoms are due to the hæmoglobin of the **blood** being converted into methæmoglobin by the action of the chlorate. They consist in hæmaturia with blood-casts and diminished secretion of urine, many of the renal tubules being filled with plugs of blood. The skin becomes discoloured or jaundiced, and death occurs with coma or convulsions.

USES.—Chlorate of potassium is chiefly used as a **local** appli-

cation to the mouth, to bring about a more healthy condition of the mucous membrane, and to cause ulceration present there to heal up. It is used in stomatitis occurring during nursing, whatever it may depend upon; in aphthæ, in cancrum oris. As a gargle it is used in follicular pharyngitis; and has been employed internally and as a local application in cases of croup, diphtheria, and spasm of the larynx. It may be used **internally** as a lotion to relieve the dryness of the throat after diphtheria and scarlatina. When taken early, it is said to lessen or arrest catarrhal conditions of the nose, throat, and larynx. It has been recommended in chronic mucous diarrhœa with whitish or mucilaginous-looking stools. It has also been used as an enema in cases of dysentery. **After absorption** into the blood it has been supposed to give off its oxygen, and thus to have a disinfectant action in cases of blood-poisoning and malignant fevers. A great part of it is excreted unchanged by the kidneys, but in large doses it decomposes the blood and converts it into methæmoglobin. It has been employed in acute and chronic bronchitis, in order to thin the secretion and promote expectoration, and as a diuretic in cases of dropsy. It was recommended by the late Sir James Simpson in 20-grain doses three times a day, to pregnant women where abortion was liable to occur from fatty degeneration of the placenta.

Potassii Permanganas, B. and U.S.P. PERMANGANATE OF POTASSIUM. $KMnO_4$, B.P. $K_2Mn_2O_8$; 314, U.S.P.

CHARACTERS.—Dark purple, slender, prismatic crystals, inodorous, with a sweet astringent taste.

PREPARATION.—By heating caustic potash and manganese dioxide together in a crucible with chlorate of potassium which yields up its oxygen to the manganese and forms manganate of potassium, $3MnO_2 + 6KHO + KClO_3 = 3K_2MnO_4 + KCl + 3H_2O$. On boiling this with water it is decomposed, permanganate being formed, and manganese dioxide being deposited. $3K_2MnO_4 + 2H_2O = K_2Mn_2O_8 + MnO_2 + 4KHO$. On decanting from the manganese dioxide, neutralising with sulphuric acid, evaporating, filtering through asbestos, and evaporating further, the salt crystallises out.

SOLUBILITY.—It is entirely soluble in cold water. A single small crystal suffices to form with an ounce of water a rich purple solution.

REACTIONS.—It gives off oxygen readily to organic substances and is decomposed, manganese dioxide being precipitated, so that the solution when mixed with a little rectified spirit and heated, becomes yellowish-brown. The crystals heated to redness decrepitate, evolve oxygen gas, and leave a black residue from which water extracts potash, recognised by its alkaline reaction and by the appropriate tests.

PREPARATION.

B.P. Liquor Potassii Permanganatis (Permanganate of Potassium 4·4 grs. in 1 fl. oz. of water or 1 per cent. solution).

Condy's fluid is a solution of 2 grains to the ounce.

ADMINISTRATION.—The solution has a disagreeable taste, and the solid permanganate of potassium gives off oxygen so readily that, if mixed with easily oxidisable substances, such as sugar,

syrup, or glycerine, the mixture may explode or take fire spontaneously. Martindale recommends that the necessary quantity of permanganate should be made into a pill with kaolin ointment consisting of equal parts of vaseline, paraffin, and kaolin.

ACTION.—Permanganate of potassium very readily parts with its oxygen, and thus **destroys organic matter**; when mixed with **cobra poison** it completely destroys the deadly power of the latter, and the mixture may be injected subcutaneously without any bad effects. When injected after the poison, however, it does not appear to come into such immediate contact with it in the tissues as to destroy it, and it therefore does not act as an antidote.

USES.—It is used to **disinfect** the stools in typhoid fever, and to disinfect the hands after making *post-mortem* examination, or after coming in contact with matters likely to convey contagion or infection (p. 105). It is applied as a lotion to wounds and sores, especially those having a foul-smelling discharge, and may be injected into the cavity of abscesses after evacuation of pus, or used to wash out the cavity of the pleura after the fluid has been removed in cases of pleurisy. In cases of ozæna it is employed to wash the nose, and as a lotion or gargle to the mouth in ulceration with fœtor, such as mercurial stomatitis, and also in diphtheria. It has been recommended internally in cases of diabetes. It is said by Ringer and Murrell to be of very great use in **amenorrhœa**, two or three grains being given in pill three or four times a day for some days before the period.

Potassa Sulphurata, B. and U.S.P. SULPHURATED POTASH, B.P.; SULPHURATED POTASSA, U.S.P.

CHARACTERS.—Solid, greenish fragments, liver-brown when recently broken, alkaline, and acrid to the taste.

SOLUBILITY AND REACTIONS.—It readily forms with water a yellow solution, which has the odour of sulphuretted hydrogen, and evolves it freely when excess of hydrochloric acid is dropped into it, sulphur being at the same time deposited. The acid fluid when boiled and filtered is precipitated yellow by perchloride of platinum, and white by chloride of barium.

IMPURITY.—Carbonate left in the preparation, or sulphate formed by decomposition.

TEST.—About three-fourths of its weight are dissolved by rectified spirit, in which both carbonate and sulphate are insoluble.

DOSE.—2 to 10 grains.

PREPARATION.

B.P.

Unguentum Potassæ Sulphuratæ (5 parts, hard paraffin 18, soft paraffin 55).

ACTION.—When applied to the skin, the ointment may be used instead of simple sulphur ointment. In the intestine sulphurated potash seems to stimulate peristaltic action, and to act as a **laxative**. Apparently also, like sulphur, it has a somewhat

stimulating action upon the **respiratory** mucous membrane, and upon the **sweat-glands.**

USES.—The ointment is used externally in cases of scabies and acne. Sulphurated potash is used as a bath in chronic rheumatism (p. 470), rheumatoid arthritis, and chronic organic nerve-disease, and as a diaphoretic in albuminuria. It has been given internally in chronic bronchitis, croup, and whooping-cough, and used as an injection into the rectum to destroy ascarides, in solutions of half a grain to a grain in the ounce of water.

Potassii Bichromas, B. and U.S.P. BICHROMATE OF POTASSIUM, $K_2CrO_4.CrO_3$, B.P. : $K_2Cr_2O_7$; 294·8, U.S.P.

CHARACTERS.—In large red, transparent, four-sided tables; anhydrous.

REACTIONS AND SOLUBILITY.—It fuses below redness; at a higher temperature is decomposed, yielding green oxide of chromium and yellow chromate of potassium, which may be separated by dissolving the latter in water. The bichromate dissolved in water gives a yellowish-white precipitate with chloride of barium, and a purplish red precipitate with nitrate of silver, and both these precipitates are soluble in diluted nitric acid. The solution also when digested with sulphuric acid and rectified spirit acquires an emerald green colour.

PREPARATIONS IN WHICH BICHROMATE OF POTASSIUM IS USED.

Acidum Chromicum. Sodæ Valerianas.

Test solution of Bichromate of Potassium, U.S.P. 1 in 10 of water.

ACTION.—In **frogs** it causes general feebleness of motion, respiration, and circulation, and sometimes convulsions. The nerve-centres are first excited and then depressed. The nerve-centres are affected before the nerves or muscles. The heart stops in diastole. In **mammals** it causes vomiting, diarrhœa, and bloody stools, great feebleness, and general clonic movements. In rabbits and guinea-pigs **convulsions** and **paralysis** occur, chiefly affecting the posterior limbs. *Post mortem* a red coloration of the muscles is observed, and the gastric and intestinal mucous membranes are congested.

USES.—It has been used by Vulpian alternately with iodide of potassium and nitrate of silver in tabes dorsalis; and in doses of $\frac{1}{2}$–$1\frac{1}{2}$ grain it is said to be useful in cases of dyspepsia simulating cancer of the stomach.

Potassii Ferrocyanidum, B. and U.S.P. FERROCYANIDE OF POTASSIUM. $K_4Fe(CN)_6.3H_2O$; 421·9.

CHARACTERS.—In large yellow four-sided tablets or prisms, permanent in the air.

SOLUBILITY.—Soluble in water, insoluble in alcohol.

REACTIONS.—The aqueous solution precipitates deep blue with persulphate of iron, brick-red with sulphate of copper, and white with acetate of lead. Heated with diluted sulphuric acid, hydrocyanic acid vapours are evolved.

Preparations for which Ferrocyanide of Potassium is used.

Acidum Hydrocyanicum Dilutum, Potassii Cyanidum.

Test solution of Ferrocyanide of Potassium. Dissolve ¼ ounce of ferrocyanide of potassium (yellow prussiate of potash) in crystals in 5 fluid ounces of distilled water and filter, B.P.; 1 in 10 of water, U.S.P.

Test solution of Ferricyanide of Potassium. Dissolve ¼ ounce of ferricyanide of potassium (red prussiate of potash) in crystals in 5 fluid ounces of distilled water and filter, B.P.; 1 in 10 of water, U.S.P.

Potassium Cyanidum, B. and U.S.P. Cyanide of Potassium. KCN; 65.

Characters.—White, opaque, deliquescent, crystalline masses having the odour of hydrocyanic acid, like which it is intensely poisonous (p. 586).

B.P. Preparation for which it is used.
Bismuthum Purificatum.

Potassii Bromidum, B. and U.S.P.—*Vide* p. 553.

Potassii Iodidum, B. and U.S.P.—*Vide* p. 559.

SODIUM. Na; 23.

Sources of Sodium Salts.—The chief source of sodium is common salt obtained by the evaporation of sea-water, or from salt mines. Two subsidiary sources are the nitrate of sodium and borax, both of which are found native.

General Reactions of Sodium Salts.—They are not precipitated by any of the ordinary reagents. The special test for them is the yellow colour which they give to flame. The mere appearance of the yellow colour is the test adopted by the British Pharmacopœia, but it is improved upon in the American Pharmacopœia, which directs that the flame should not appear more than transiently red when observed through a blue glass. In this way sodium salts are both more readily distinguished from those of potassium, and the presence of the slightest impurity is easily observed; for sodium salts are so widely distributed in nature, and the yellow colour which they give to the flame is so bright, that minute quantities of sodium mixed with potassium may disguise the violet colour which the potassium gives, although it should be present in much greater quantity than the sodium. To distinguish between potassium salts and sodium salts, it is therefore necessary to look at the flame through a blue glass, which cuts off the yellow rays emitted by the sodium of the flame, and thus allows the violet ones of the potassium to be seen.

PREPARATION OF SODIUM SALTS.

	Prepared from	By
Sodium chloride .	Sea-water . . .	Evaporation. Or found native.
Sodium sulphate .	Sodium chloride .	Heating with sulphuric acid in the preparation of hydrochloric acid.
Sodium carbonate .	Sodium sulphate .	Roasting with calcium carbonate and coal.
Sodium . . .	Sodium carbonate .	Igniting with charcoal.
Sodium ethylate (Liquor)	Sodium . . .	Dissolving in ethylic alcohol.
Dried sodium carbonate	Sodium carbonate .	Heating.
Sodium bicarbonate .	Ditto .	Mixing with dry carbonate and saturating with carbonic acid.
Caustic soda . .	Ditto .	Decomposing by lime.
Sodium acetate .	Ditto .	Neutralising with acetic acid.
Effervescent citro-tartrate	Ditto .	Heating dry carbonate with tartaric and citric acids.
Tartrate of soda and potash (soda tartarata)	Ditto .	Neutralising solution with acid tartrate of potassium, evaporating and crystallising.
Sodium benzoate, U.S.P.	Ditto .	Neutralising a hot solution with benzoic acid and crystallising.
Sodium phosphate .	Ditto .	Decomposing bone-ash with sulphuric acid, and saturating the acid phosphate of calcium thus obtained with sodium carbonate.
Sodium hypophosphite	Ditto .	Decomposing hypophosphite of lime with sodium carbonate.
Liquor sodæ chlorinatæ	Ditto .	Passing chlorine through its solution.
Sodium valerianate .	Ditto .	Neutralising by valerianic acid.
Sodium salicylate, B. and U.S.P.	Ditto .	Neutralising solution by salicylic acid with slight excess of acid and evaporating.
Sodium sulphocarbolate, B. and U.S.P.	Ditto .	Decomposing by barium sulphocarbolate. The barium sulphocarbolate is prepared by mixing equal parts of carbolic and strong sulphuric acid, allowing them to stand for some days, diluting and neutralising with barium carbonate.
Sodium bisulphite, U.S.P.	Sodium carbonate .	Saturating its solution with sulphurous acid.
Sulphite, B. and U.S.P.	Sodium bisulphite .	Adding an equal weight of sodium carbonate to the bisulphite prepared as above.
Hyposulphite, U.S.P. and B.P., App.	Sulphite . . .	Heating with sulphur.
Borax . . .	—	Found native.
Nitrate . . .	—	Found native.
Arseniate . . .	Carbonate and nitrate	Fusing with arsenious acid.

GENERAL IMPURITIES OF SODIUM SALTS.—As sodium carbonate is prepared from sodium sulphate, and the latter from sodium chloride, sulphates and chlorides may be present as impurities in it. As the other sodium salts are chiefly obtained from the carbonate, chlorides and sulphates also come to be present as

impurities in them. They also occur even in the nitrate of sodium found native.

General Tests for Impurities in Sodium Salts.—In order to distinguish between salts of potassium and sodium, as well as to prove the absence of potassium as an impurity, the B.P. directs that the solutions of sodium salts, when acidulated, should not give a precipitate with perchloride of platinum. The U.S.P. directs that the yellow colour which sodium salts give to the flame should not appear more than transiently red when seen through a blue glass. The absence of chlorides and sulphates is ascertained by the usual tests (pp. 594, 595), and the absence of metals by the want of any colour or precipitate on the addition of hydrosulphuric acid or ammonium sulphide.

General Action of Sodium Salts.—Salts of sodium **diffuse** more slowly than those of potassium. They are neither absorbed nor excreted so readily, and have not a marked diuretic action. When locally applied to **muscle** and **nerve** in large doses they paralyse both, but not so powerfully as salts of potassium, nor have they such a paralysing action upon the involuntary muscle, either of the **heart** or the **intestine**. In large doses they lengthen the muscular curve, and increase the length of the curves produced by calcium and strontium instead of shortening them, like potassium (p. 142).

Urate of sodium is less soluble than urate of potassium or lithium. It is therefore less readily excreted, and forms the nodules known by the name of chalk-stones in gouty patients.

B.P. Sodium. Sodium. Na; 23. The metallic element sodium as met with in commerce. It should be preserved in well-stoppered bottles under mineral naphtha.

Characters.—A soft metal, rapidly oxidising in the air, but showing a bright metallic surface when freshly cut.

Reactions.—It attacks water or alcohol, with evolution of hydrogen gas, little or no insoluble matter remaining. Twenty-three grains, cautiously dissolved in water, require for neutralisation at least 975 grain-measures of the volumetric solution of oxalic acid.

Preparation.

Liquor Sodii Ethylatis.

B.P. Liquor Sodii Ethylatis. Solution of Ethylate of Sodium.—It contains 19 per cent. of the solid salt, NaC_2H_5O.

Characters.—A colourless liquid of syrupy consistence, becoming brown by keeping. Specific gravity 0·867.

Preparation.—By dissolving metallic sodium (1) in ethylic alcohol (20) contained in a flask which is kept cool in a stream of cold water. The solution should be recently prepared.

Reactions.—When heated it boils and gives off alcoholic vapours, leaving a white salt which, on being strongly heated, chars. If the white salt be

mixed with water and heated, it yields alcohol, and the solution, on evaporation, leaves a white residue consisting almost wholly of caustic soda.

ACTION.—It is a powerful **caustic.**

USE.—To destroy nævi. It should be applied by means of a glass rod to the nævus for two or three days successively, and then discontinued until the scab which forms has become detached, after which the treatment should be resumed.

Sodii Chloridum, B. and U.S.P. CHLORIDE OF SODIUM. COMMON SALT. NaCl; 58·4.

CHARACTERS.—In small white crystalline grains, or transparent cubic crystals, free from moisture. It has a purely saline taste, and imparts a yellow colour to flame.

SOLUBILITY AND REACTIONS.—Is soluble in water. The solution gives the reaction of a chloride (p. 594), and does not give that of potassium but of sodium (p. 617).

PREPARATIONS IN WHICH CHLORIDE OF SODIUM IS USED.

Acidum Hydrochloricum. Hydrargyri Perchloridum.
Hydrargyri Subchloridum.

ACTIONS.—Although chloride of sodium is not much used as a remedy, it is most important as a **food.** It forms a large proportion of the salts of the body, and no doubt plays a very important part in tissue-change. When persons are deprived of it for a length of time the longing for it becomes intense, and animals will go very great distances to obtain it. When mixed with water, in the proportion of **0·65 to 100, the solution does not destroy animal tissues** like water alone, and may be mixed with blood without destroying the corpuscles (*vide* p. 600). Strong solutions, however, are intensely irritating. When injected into the lymph-sac of a frog it causes increased **diapedesis** of the red corpuscles, which then pass out through the vessels in considerable numbers. It is possible that an increase in the proportion of sodium chloride may have something to do with the production of scurvy, as this disease appears to be relieved by salts containing another base than sodium and another acid radical than chlorine.

USES.—Externally it is used as a **stimulant** to the skin in the form of baths (pp. 459 and 469). A solution of salt of ½ to 1 per cent. has been recommended by Kühne to wash wounds and raw surfaces in place of water, as it does not destroy the vitality of the tissues, and a similar solution may be used instead of water to wash out the nasal cavities, either alone or mixed with other medicaments. When taken in considerable quantities it produces vomiting, and may be used as an **emetic,** either alone or to aid the action of other emetics. Half a teaspoonful of dry salt, repeated until nausea is produced, is said sometimes to arrest hæmoptysis. It appears to diminish the secretion of mucus, and may be given to children suffering from

worms, where the intestinal mucus is excessive and affords a nidus for the parasites.

A solution (ʒss in ℥j water) flavoured with liquorice, in table-spoonful doses every two hours, sometimes proves very useful in causing absorption of pleuritic serous exudation. It is contra-indicated when the exudation is purulent.

After hæmorrhage there is generally excessive thirst, and the addition of chloride of sodium to the water drunk by the patient has been recommended in order to prevent destruction of the blood-corpuscles which might arise from the absorption of small amounts of pure water. During convalescence patients sometimes exhibit a desire for salt and indigestible food, which, if given, would probably derange the digestion, but the craving may be allayed by giving salt alone. It has been used in bilious diarrhœa, in doses of 10 to 60 grains, three or four times a day.

As an **enema** to destroy ascarides it is frequently used. The proportion generally is 1 or 2 tablespoonfuls to the pint of water.

Sodii Carbonas, B. and U.S.P. CARBONATE OF SODIUM. $Na_2CO_3.10H_2O$; 286.

Obtained from the ashes of marine plants, or produced by chemical decomposition with chloride of sodium.

CHARACTERS.—In transparent, colourless, laminar crystals, of a rhombic shape, efflorescent, with a harsh alkaline taste and strong alkaline reaction.

REACTIONS.—By heat it undergoes aqueous fusion, and then dries up, losing 63 per cent. of its weight.

$$\left.\begin{array}{l}\text{20 grains}\\ \text{Carbonate of Sodium}\end{array}\right\}\text{neutralise}\left\{\begin{array}{l}\text{9·7 grains Citric Acid.}\\ 10\tfrac{1}{2}\text{ grains Tartaric Acid.}\end{array}\right.$$

DOSE.—5 to 30 grains.

PREPARATIONS.

B.P.	DOSE.
Sodii Carbonas Exsiccata. Dried carbonate of sodium (used for pills)	3–10 grs.

USES.—It is not much used as a remedy. Its chief use is in the preparation of other sodium salts. A dilute solution of it may be used as a wash to the skin to remove itching. In cases of anæmia it may be combined with ferri sulphas exsiccata, 4 grains of each, in pill.

Soda Caustica, B.P. ; Soda, U.S.P. CAUSTIC SODA, B.P. ; SODA, U.S.P.—Hydrate of sodium, NaHO, 40, with some impurities.

CHARACTERS.—Hard, greyish-white pencils or fibrous pieces, deliquescent in moist air, dry and efflorescent in dry air, very alkaline and corrosive.

REACTIONS AND TESTS.—It gives the tests of sodium (p. 617), and not of potassium. Its solution in water, acidulated by nitric acid, effervesces only

slightly (limit of carbonate) and gives only scanty white precipitates with nitrate of silver and chloride of barium (limit of chlorides and sulphates).

IMPURITIES.—Carbonate, chlorides, sulphates.

PREPARATION CONTAINING CAUSTIC SODA.

Liquor Sodæ ....18·8 grains in 1 fluid ounce.

USE.—It is used as **caustic** like potash, but has less affinity for water, and so does not take it from the tissues and destroy them so powerfully. At the same time it has less tendency to run over adjacent parts.

Liquor Sodæ, B. and U.S.P. SOLUTION OF SODA.—An aqueous solution of hydrate of sodium (NaHO; 40) containing about 3 per cent. of the hydrate, U.S.P. (4·1 per cent. B.P.).

CHARACTERS.—Like those of liquor potassæ (p. 607), but it is not precipitated by tartaric acid nor by perchloride of platinum.

USES.—Is used in preparing ferric oxide and in other pharmaceutical processes, as it is cheaper than solution of potash. Internally it may act on the blood, rendering it and the secretions more alkaline, but it will not alter nutrition in the way that potassium salts do.

Sodii Bicarbonas, B. and U.S.P. BICARBONATE OF SODIUM. $NaHCO_3$; 84.

CHARACTERS.—In powder, or small opaque irregular scales, white, of a saline and not unpleasant taste.

REACTIONS.—It gives the reactions showing the presence of sodium, and of carbonic acid. It is distinguished from carbonate by its solution in cold water giving a white and not a coloured precipitate with solution of perchloride of mercury.

20 grains of Bicarbonate of Sodium neutralise { 16·7 grains of Citric Acid, or 17·8 grains of Tartaric Acid.

DOSE.—10 to 60 grains.

PREPARATIONS CONTAINING BICARBONATE OF SODIUM.

B.P.		DOSE.
Liquor Sodæ Effervescens (soda-water)	30 grains in 1 pint	$\frac{1}{6}$–1 pint.
Sodii Citro-tartras Effervescens	17 parts in 31	6 grs. to $\frac{1}{4}$-oz.
Trochisci Sodii Bicarbonatis	5 grs. in each lozenge	1 to 6.

U.S.P.

Sodii Bicarbonas Venalis (for external use).
Mistura Rhei et Sodæ ....2 dr. to 3 oz.
Pulvis Effervescens Compositus ....one or two powders.

U.S.P. Sodii Bicarbonas Venalis. COMMERCIAL BICARBONATE OF SODIUM.—Should contain 95 per cent. of pure bicarbonate, which it resembles in appearance and tests.

U.S.P. Mistura Rhei et Sodæ. MIXTURE OF RHUBARB AND SODA.—Bicarbonate of sodium 3, fluid extract of rhubarb 3, spirit of peppermint 3, water q.s. to make 100.

U.S.P. Pulvis Effervescens Compositus. COMPOUND EFFERVESCING POWDER.—Bicarbonate of sodium 8, tartrate of potassium and sodium 24, mixed to make a powder of 160 grains; tartaric acid, in separate powder, 35 grains.

USES.—Bicarbonate of sodium has a slight local irritant

action. It may be used as a wash in cases of itching skin-diseases, e.g. prurigo, and as a lotion to eczema. The strength is 2 grains to the ounce, and it is applied like water-dressing.

A solution of this strength when used to rinse the mouth sometimes relieves the pain of toothache, and also relieves headache, either temporal or occipital, depending on decayed teeth, even though no pain should be felt in the tooth itself.

It may also be used to prevent injury to the teeth from acid tonics.

Mixed with tincture of opium, and introduced into the cavity of a decayed tooth by means of a pledget of cotton-wool, it will often arrest the pain of toothache. When swallowed it stimulates the secretion of gastric juice, and is a most efficient remedy when given from ten minutes to half an hour before meals, in cases of atonic **dyspepsia**, where the patient complains of weight or pain at the pit of the stomach, pain between the scapulæ, and much flatulence unaccompanied by constipation. In such cases it is often advantageous to combine it with a bitter tonic and some carminative. As dyspepsia often occurs in persons engaged in business who cannot carry mixtures about with them, the lozenges (B.P.) are very useful, for they can be easily carried about and taken when necessary.

It also relieves frontal **headache**, unaccompanied by constipation, where the headache is situated just at the junction of the forehead with the hairy scalp. Frontal headache, lower down, just above the eyebrows, is better treated by nitro-hydrochloric acid (p. 576). In persons who suffer from great acidity after meals, it may be used as an **antacid**. A solution of $\frac{1}{2}$ or 1 grain to the ounce of water or milk is exceedingly useful in the diarrhœa and marasmus of infants.

It is also serviceable in cases of diabetes, to lessen the amount of sugar. It renders the bronchial secretion less tenacious, but is not so useful as bicarbonate of potassium. The lozenges are very convenient in such cases.

It seems to have less tendency than potash to produce catarrh of the stomach, and may be used for a longer time (p. 606).

As sodium naturally exists in large quantity in the blood, the amount we can add is but a small fraction of that quantity, and its alterative action is very slight. It will increase the alkalinity of the blood, and has been given instead of bicarbonate of potassium in acute rheumatism, but it is perhaps not so good. The urate of sodium is not so soluble as that of potassium, so sodium is not so good in the uric acid diathesis (Garrod), and its diuretic power is also less.

B.P. Sodii Citro-Tartras Effervescens. EFFERVESCENT CITRO-TARTRATE OF SODIUM.

CHARACTERS.—A granular powder which effervesces on the addition of water.

DOSE.—60 grains to $\frac{1}{4}$-ounce.

USE.—If absorbed there may be some slight difference between the effect of this salt and of tartarated soda, which contains some potash, but this is very slight, and of no importance. It is used only for its **laxative** effect. It is both pleasanter to take than tartarated soda, and it is less likely to cause unpleasant feelings in the stomach.

Soda Tartarata, B.P.; Potassii et Sodii Tartras, U.S.P. TARTARATED SODA, B.P.; TARTRATE OF POTASSIUM AND SODIUM, U.S.P. ROCHELLE SALT. $NaKC_4H_4O_6.4H_2O$; 282.

CHARACTERS.—In colourless, transparent prisms or halves of prisms, of the right rhombic order, generally eight-sided; tasting like common salt.

IMPURITY.—Bitartrate of potassium.

TEST.—Entirely soluble in cold water.

REACTIONS.—Heated with sulphuric acid it blackens, evolving inflammable gases and the odour of burnt sugar (tartrate). It imparts a yellow colour to flame (sodium). A strong solution gives a crystalline precipitate with a small quantity of acetic acid (potassium).

DOSE.—As a purgative, $\frac{1}{4}$ to $\frac{1}{2}$ ounce; as a diuretic, 30 to 60 grains.

USES.—In large doses it retains water, quickens peristalsis, acts as a **purgative**, and is chiefly used as such. In small doses it is absorbed from the intestines, is converted in the blood into carbonate of potassium and sodium, causes **diuresis** and renders the urine alkaline. It may be used as a remote antacid.

Sodii Acetas, B.P. Appendix, and U.S.P. ACETATE OF SODIUM, U.S.P. $NaC_2H_3O_2.3H_2O$; 136.

USES.—In testing and in preparing acetic ether.

Borax, B.P.; Sodii Boras, U.S.P. BORAX, B.P.; BORATE OF SODIUM, U.S.P. BIBORATE OF SODIUM. $Na_2B_4O_7.10H_2O$; 382.

A native salt. It is also made artificially by boiling together, in proper proportions, boric acid and carbonate of sodium.

CHARACTERS.—In transparent, colourless crystals, sometimes slightly effloresced, with a weak alkaline reaction.

SOLUBILITY.—Insoluble in rectified spirit, soluble in water.

REACTIONS.—A hot saturated solution, when acidulated with any of the mineral acids, lets fall, as it cools, a scaly crystalline deposit (boric acid), the solution of which in spirit burns with a green flame.

DOSE.—5 to 40 grains.

PREPARATIONS.

B.P.

Glycerinum Boracis.......1 part in 6 by weight (= 1 oz. in 4 fluid oz. glycerine).
Mel Boracis ....56 grains in 1 oz.

Used also to prepare boric acid.

USES.—Borax destroys low vegetable organisms and prevents their germination. It thus acts as a **disinfectant**. Applied to the skin it removes the epidermis, and may be used for this purpose instead of soap. It is used as a lotion in acne. It forms a useful wash to remove scurf from the head, chloasma or liver spots, and to allay itching in urticaria, psoriasis, impetigo, and pruritus pudendi, scroti, and ani; it is also used in acute eczema in a solution of 1 per cent. with 1 per cent. of acetate of alum. In intertrigo it may be dusted on in a mixture with 5 per cent. of oxide of bismuth and starch. It is much employed in aphthous conditions of the mouth and throat, either alone or combined with chlorate of potassium. It may be given simply in solution, or in the form of the honey or glycerine. As an injection it is useful in leucorrhœa and gonorrhœa.

It has been supposed to have a special action upon the **uterus**, and has been employed in amenorrhœa, dysmenorrhœa, and puerperal fever and convulsions. On account of its asserted power to increase the uterine contraction, it ought either to be avoided or employed with care during pregnancy. Borax is useful in some cases of epilepsy in doses of 10 to 15 grains three times a day. It acts as a solvent to benzoic acid.

Sodii Sulphas, B. and U.S.P. SULPHATE OF SODIUM. GLAUBER'S SALT. $Na_2SO_4.10H_2O$; 322.

CHARACTERS.—In transparent, oblique prisms. It has a salt and bitter taste and effloresces on exposure to the air.

SOLUBILITY.—It is soluble in water, insoluble in spirit.

REACTIONS.—It gives the reactions of sodium (p. 617) and of a sulphate (p. 595).

PREPARATION, B.P.—May be obtained from the residue left in the manufacture of hydrochloric acid, by neutralising it with carbonate of sodium, and crystallising from solution in water.

DOSE.—$\frac{1}{4}$ to 1 ounce.

USES.—Sulphate of sodium, when introduced into the stomach, is supposed to excite peristaltic movements in it, and to have a similar action upon the intestine. It produces in the intestine a secretion of watery fluid, and acts as a **purgative**. It is used either alone, or mixed with bicarbonate of sodium, in ulcer of the stomach, chronic gastritis, and dilatation of the stomach. A mixture of sulphate and bicarbonate of sodium has been used in imitation of the Carlsbad salts obtained by evaporation of the natural mineral water of Carlsbad. The mixture, or the natural salts, ought to be taken dissolved in warm water immediately after rising, and it is better to sip the solution at intervals, while dressing, than to drink the whole off at a draught (p. 406). One-third of a teaspoonful of the crystallised salts in a large tumblerful of warm water, taken immediately on rising, is frequently sufficient to produce one free action of the bowels after breakfast, and no more. This quantity of salts, with a

smaller quantity of water, may have no action; and if a smaller quantity of water be used along with a larger quantity of salts it not unfrequently happens that several scanty motions occur during the day, with considerable discomfort in the abdomen.

Carlsbad water, natural or artificial, is also useful in bilious disorders, and in persons of a gouty diathesis. A gentle course will often remove the dulness, irritability, and other symptoms which accompany biliary derangements or precede a gouty attack. It may be used, also, with advantage in chronic constipation and tendency to congestion of the brain or of the abdominal and pelvic organs. A continued course of the water is exceedingly beneficial in cases of excessive obesity, and also in diabetes mellitus.

The Carlsbad waters contain a number of other salts which are not crystallised out, and they often prove much more efficient when drunk at the springs than when the solution of the salts is taken by patients at their own homes. The great benefit which is often obtained from a course of the waters at Carlsbad is no doubt due in great measure to the diet and regimen which patients will follow there in company with others, but which nothing would induce them to conform to while at home.

Sodii Sulpho-carbolas, B. and U.S.P. SULPHO-CARBOLATE OF SODIUM. $NaC_6H_5SO_4.2H_2O$.

CHARACTERS.—Colourless, transparent, rhombic prisms, inodorous, or nearly so, with a cooling, saline, and somewhat bitter taste.

SOLUBILITY.—Readily soluble in water, less so in spirit.

REACTIONS.—On ignition it gives off vapours of carbolic acid, and the residue dissolved in water gives a precipitate with chloride of barium (sulphate). It gives a yellow colour to flame. The watery solution is neutral to test-paper, and gives a violet colour with perchloride of iron. It is not at once rendered turbid by chloride of barium.

DOSE.—10–15 grains.

ACTION.—**Antiseptic** and mildly astringent.

USES.—It arrests fermentation in the stomach, and when given before meals is useful in flatulence and acidity occurring in phthisical patients. It may be combined with bitters. It is used in septic conditions.

Sodii Phosphas, B. and U.S.P. PHOSPHATE OF SODIUM. $Na_2HPO_4.12H_2O$; 358.

CHARACTERS.—In transparent, colourless, rhombic prisms, terminated by four converging planes, efflorescent, tasting like common salt. It imparts a yellow colour to flame.

REACTIONS.—Its solution has a faintly alkaline reaction; it gives a yellow precipitate with nitrate of silver, the resulting fluid acquiring an acid reaction (phosphate).

DOSE.—As a purgative, ½ to 1 ounce. As an alterative, 20 to 40 grains.

USES.—It is used as a **purgative** in children and in delicate persons, both because it acts gently and has little or no taste. It may be easily given to children in a little soup without their knowing it.

It has been used in fevers as a purgative, and in rickets in order to supply phosphoric acid to the bones. It has been found especially useful in children with hepatic derangement, as shown either by white or green stools, or by jaundice. The dose for them is 3 to 10 grains given in food or milk.

U.S.P. Sodii Chloras. CHLORATE OF SODIUM. $NaClO_3$; 106·4.

CHARACTERS.—Colourless, transparent tetrahedrons of the regular system; permanent in dry air, odourless, having a cooling saline taste and a neutral reaction.

SOLUBILITY.—Soluble in 1·1 parts of water, and in 40 parts alcohol at 15° C. (59° F.); in 0·5 parts of boiling water, and in 43 parts of boiling alcohol.

REACTIONS.—When heated the salt melts, and afterwards gives off a portion of its oxygen, finally leaving a residue of sodium chloride which gives the reactions peculiar to it (p. 620).

USES.—Similar to those of chlorate of potassium (*vide* p. 613). As it is more soluble, stronger solutions can be employed.

Sodii Hypophosphis, B. and U.S.P. HYPOPHOSPHITE OF SODIUM. $NaH_2PO_2.H_2O$; 106.

CHARACTERS.—Small, colourless or white rectangular plates, or a white granular powder, deliquescent on exposure to air, odourless, having a sweetish saline taste and a neutral reaction.

SOLUBILITY.—Soluble in 1 part of water and in 30 parts of alcohol at 15° C. (59° F.); in 0·12 parts of boiling water, and in 1 part of boiling alcohol.

REACTIONS.—When heated in a dry test-tube the salt loses water, and then evolves a spontaneously inflammable gas (phosphoretted hydrogen), burning with a bright yellow flame. A fragment of the salt imparts to a non-luminous flame an intense yellow colour, not appearing more than transiently red when observed through a blue glass. On triturating or heating the salt with an oxidising agent the mixture will explode.

DOSE.—1 to 10 grains (5 to 10 grs. B.P.).

PREPARATION.

U.S.P.

Syrupus Hypophosphitum.

USES.—It is said to have a stimulating action upon the **nervous system**, and to increase digestion and **nutrition**. It is chiefly given in the earlier stages of phthisis (*vide* p. 717), and in anæmia and nervous debility.

U.S.P. Liquor Sodii Silicatis.

CHARACTERS.—An almost colourless, slightly yellow, viscid liquid, with a sharp saline taste and an alkaline reaction.

REACTIONS.—It imparts an intense yellow colour to a non-luminous flame. A small quantity should not produce any caustic effect on the skin (showing the absence of excess of alkali).

USE.—It is used for making bandages, which are thus rendered lighter than plaster-of-paris, and stronger than starch, bandages.

U.S.P. Sodii Benzoas. BENZOATE OF SODIUM. $NaC_7H_5O_2.H_2O$; 162.

CHARACTERS.—A white, semi-crystalline, or amorphous powder, efflorescent on exposure to air, odourless, or having a faint odour of benzoin, of a sweetly astringent taste, free from bitterness, and having a neutral reaction.

TESTS.—When heated the salt melts, emits vapours having the odour of benzoic acid, then chars, and finally leaves a blackened residue of an alkaline reaction and exhibiting the reactions of sodium (p. 617). On mixing an aqueous solution of the salt with a dilute solution of ferric sulphate a flesh-coloured precipitate is produced.

DOSE.—10 to 20 grains.

USES.—It has been strongly recommended as a remedy in phthisis, and has also been used in puerperal fever and to eliminate uric acid in gout.

Sodii Iodidum.—*Vide* p. 563.

Sodii Bromidum.—*Vide* p. 555.

U.S.P. Sodii Pyrophosphas. PYROPHOSPHATE OF SODIUM. $Na_4P_2O_7.10H_2O$; 446.

CHARACTERS.—Colourless, translucent, monoclinic prisms, permanent in the air, odourless, having a cooling, saline, and feebly alkaline taste, and a slightly alkaline reaction.

SOLUBILITY.—Soluble in 12 parts of water at 15° C. (59° F.) and in 1·1 parts boiling water; insoluble in alcohol.

REACTIONS.—Its aqueous solution with excess of test-solution of nitrate of silver gives a white precipitate and a neutral filtrate.

ACTION.—Its actions in medicinal doses appear to be nearly the same as those of the phosphate, but probably it would have a greater influence on the nervous system.

USES.—To prepare the pyrophosphate of iron.

Sodii Salicylas, B. and U.S.P. SALICYLATE OF SODIUM. $2NaC_7H_5O_3.H_2O$; 338.

CHARACTERS.—Small, white, crystalline plates, or a crystalline powder, permanent in the air, odourless, having a sweetish saline and mildly alkaline taste and a feebly acid reaction.

SOLUBILITY.—Soluble in 1·5 parts of water and in 6 parts of alcohol at 15° C. (59° F.); very soluble in boiling water and in boiling alcohol.

REACTIONS.—When heated the salt gives off inflammable vapour and leaves an alkaline residue amounting to between 30 and 31 per cent. of the original weight, and which gives the reactions of sodium carbonate.

Dose.—In rheumatism with high temperature 10 to 20 grains every two to four hours. The addition of some aromatic spirit of ammonia, or alcohol in some form, tends to lessen the cardiac depression which the salicylate alone may cause.

Action and Uses.—It agrees in its action with salicylic acid, excepting that it has no power to destroy low organisms. In febrile conditions, and especially in acute rheumatism, it greatly lowers the **temperature** and lessens the pain. Its use should be continued for some time after apparent convalescence, as the temperature is apt to rise again when the administration of the remedy ceases. It often gives relief in tonsillitis. In small doses it is useful in chronic rheumatism. In doses of ½ to 2½ grains every quarter or half hour it will often cut short headaches. The symptoms of its physiological action are the same as those of salicylic acid (see p. 819)—ringing in the ears, &c. (pp. 228 and 229). These symptoms may be lessened by ergot, hydrobromic acid, or bromides. It renders the **bile** more watery, and so may be used to prevent gall-stones; it is sometimes very useful in diabetes.

U.S.P. Sodii Santoninas. Santoninate of Sodium. $2NaC_{15}H_{19}O_4.7H_2O$; 698.

Preparation.	Dose.
Trochisci Sodii Santoninatis	1 grain in each, 1–5 lozenges

Characters.—Colourless, transparent, tabular, rhombic crystals, slowly coloured yellow by exposure to light, slightly efflorescent in dry air, odourless, having a mildly saline and somewhat bitter taste, and a slightly alkaline reaction.

Reactions.—The aqueous solution, on the addition of hydrochloric acid, deposits a crystalline precipitate, which is soluble in chloroform, and which yields, with alcoholic solution of potassa, a scarlet-red liquid gradually becoming colourless.

Dose.—8 to 10 grains.

Uses.—This substance has been introduced into the U.S.P. as an **anthelmintic.**

Sodii Sulphis, B. and U.S.P. Sulphite of Sodium. $Na_2SO_3.7H_2O$; 252.

Characters.—Colourless, transparent, monoclinic prisms, efflorescent in dry air, odourless, having a cooling saline and sulphurous taste.

Reactions of Sodium Sulphite, Bisulphite, and Hyposulphite.—They all evolve sulphurous acid vapours, recognised by their giving the smell of burning sulphur on the addition of hydrochloric acid to an aqueous solution. The hyposulphite is distinguished from the sulphites by the acid causing sulphur to be deposited from the solution, and thus rendering it turbid, whilst solutions of the sulphites remain clear. The sulphites are distinguished from each other by the bisulphite having an acid and the sulphite a neutral or feebly alkaline reaction.

Dose.—5 to 20 grains, or even up to 1 drachm (3·9 gm.).

USES.—A solution of 1 part in 8 of water is used in cases of aphthæ in the mouth; it has been given also to destroy sarcinæ and torulæ in cases of yeasty vomiting (*vide* Sulphurous Acid, p. 572). In some cases of boils the sulphite and hyposulphite in 15 to 20 grain doses every 2 or 3 hours are said to have effected a cure.

U.S.P. Sodii Bisulphis. BISULPHITE OF SODIUM. $NaHSO_3$; 104.

CHARACTERS.—Opaque, prismatic crystals, or a crystalline or granular powder, slowly oxidised, and losing sulphurous acid on exposure to air, having a faint sulphurous odour, and a disagreeable sulphurous taste.

DOSE.—15 to 60 grains.

USES.—The same as those of the sulphite.

U.S.P. and Appendix B.P. Sodii Hyposulphis. HYPOSULPHITE OF SODIUM. $Na_2S_2O_3.5H_2O$; 248.

CHARACTERS.—Large, colourless transparent prisms or plates; no smell; cooling, rather bitter taste.

USE.—It is an antiseptic and deodoriser like the sulphites. Chiefly used as a reagent to estimate iodine (*vide* p. 556).

B.P. Sodii Valerianas. VALERIANATE OF SODIUM. $NaC_5H_9O_2$.

CHARACTERS.—In dry white masses, without alkaline reaction, entirely soluble in rectified spirit, and giving out a powerful odour of valerian on the addition of dilute sulphuric acid.

PREPARATION.—By distilling amylic alcohol with a mixture of dilute sulphuric acid and an aqueous solution of bichromate of potassium: $2K_2Cr_2O_7 + 8H_2SO_4 = 2(Cr_2(SO_4)_3) + 2K_2SO_4 + 8H_2O + 3O_2$; and $C_5H_{11}HO + O_2 = HC_5H_9O_2 + H_2O$. The valerianic acid thus obtained is saturated with a solution of soda and dried: $HC_5H_9O_2 + NaHO = NaC_5H_9O_2 + H_2O$.

DOSE.—$\frac{1}{2}$ to 5 grains.

PREPARATION IN WHICH VALERIANATE OF SODIUM IS USED.

Zinci Valerianas.

USE.—As an **antispasmodic** in hysteria. It is chiefly used for making the zinc salt.

LITHIUM. Li; 7.

SOURCES OF LITHIUM.—Native silicates and phosphates of lithium and other metals.

REACTION.—It is recognised by the *red* colour which it gives to flame. This appears to be more brilliant when the salt is first converted into chloride by addition of hydrochloric acid.

GENERAL IMPURITIES OF LITHIUM.—Alkalis, alkaline salts, and metals.

PREPARATION OF LITHIUM SALTS.

Lithium Salt	Is prepared from	By
Carbonate, B. and U.S.P.	Lithium chloride obtained from minerals	Precipitating with carbonate of ammonium.
Citrate, B. and U.S.P.	Lithium carbonate .	Dissolving in citric acid.
Benzoate, U.S.P. .	Ditto .	Neutralising in hot solution with benzoic acid, filtering, and evaporating to dryness, or crystallising.
Salicylate, U.S.P. .	Ditto .	Neutralising hot solution with salicylic acid, filtering, and evaporating.
Bromide, U.S.P. .	Ditto .	Neutralising with sulphuric acid, and decomposing the sulphate thus obtained by bromide of potassium.

TESTS.—The alkalis are detected by igniting the lithium salt and converting the carbonates which remain (when the acid has been an organic one, as citric or salicylic) into chloride by the addition of hydrochloric acid. On evaporating the filtered solution to dryness, 1 part of the residue should be completely soluble in 3 parts of alcohol, and should give no precipitate on the addition of an equal volume of stronger ether, U.S.P. (Alkaline salts, if present, would give a precipitate.) A solution in water of another portion of the residue should give no precipitate with a solution of oxalate of ammonium (absence of alkaline earths), and no precipitate or colour with hydrosulphuric acid or ammonium sulphide (absence of metals, U.S.P.).

GENERAL ACTION OF LITHIUM SALTS.—The action of lithium upon muscle, nerves, and nerve-centres is very much like that of potassium (*vide* p. 605), but is more powerful.

Lithii Carbonas, B. and U.S.P. CARBONATE OF LITHIUM. Li_2CO_3; 74.

CHARACTERS.—In white powder or in minute crystalline grains, alkaline in reaction.

SOLUBILITY.—It is soluble in 100 parts of cold water, insoluble in alcohol.

REACTIONS.—It dissolves with effervescence in hydrochloric acid; and the solution evaporated to dryness leaves a residue of chloride of lithium, which communicates a red colour to the flame of a spirit-lamp, and redissolved in water yields a precipitate with phosphate of sodium.

DOSE.—3 to 6 grains.

PREPARATION.

B.P.

Liquor Lithiæ Effervescens. LITHIA WATER (10 grains in 1 pint of water saturated with carbonic acid), given in quantities of 5 to 10 fluid ounces.

USES.—The urates of lithium being much more soluble than those of either potassium or sodium, lithia is often employed in-

preference to these other alkalis in gout. It is given internally in order to aid in the elimination of uric acid by the kidneys, to prevent the gouty paroxysm, and to lessen the acidity of the urine, to prevent the deposit of uric acid gravel or calculi in the kidneys or bladder, and also to aid in their solution when already formed. It is applied locally to parts affected with gouty inflammation, in order to aid in the solution and absorption of the urate of sodium in the tissues. For this purpose it may be applied to stiff joints and chalk-stones, whether covered by the skin or already laid bare by ulceration. A solution of lithia, five grains to the ounce, is kept constantly applied to the part for several weeks together.

Lithii Citras, B. and U.S.P. Citrate of Lithium $Li_3C_6H_5O_7$; 210.

Characters and Tests.—A white amorphous powder, deliquescent, and soluble in water without leaving any residue.

Reactions.—Heated to redness it blackens, evolving inflammable gases; and leaving a residue of lithium carbonate which gives the usual reactions.

Dose.—5-10 grains.

Use.—It has a similar action to the carbonate, and may be used in its stead where we wish to avoid any local action upon the stomach itself.

U.S.P. Lithii Benzoas. Benzoate of Lithium. $LiC_7H_5O_2$; 128.

Characters.—A white powder, or small shining scales permanent in the air, odourless or having a faint benzoin-like odour; of a cooling sweetish taste, and a faintly acid reaction.

Reactions.—When heated, the salt fuses; at a higher temperature it chars, emits inflammable vapours having a benzoin-like odour, and finally leaves a black residue of an alkaline reaction, and imparting a crimson colour to a non-luminous flame. On mixing the aqueous solution with a dilute solution of ferric sulphate, a flesh-coloured precipitate is produced.

Dose.—8-30 grains (0·5–2 gm.).

Uses.—It has been used as a remedy for gout and uric acid.

U.S.P. Lithii Bromidum.—*Vide* p. 556.

U.S.P. Lithii Salicylas. Salicylate of Lithium. $2LiC_7H_5O_3.H_2O$; 306.

Characters.—A white powder, deliquescent on exposure to air, odourless, or nearly so, having a sweetish taste and a faintly acid reaction.

Solubility.—Very soluble in water and in alcohol.

Reactions.—When strongly heated the salt chars, emits inflammable vapours, and finally leaves a black residue having an alkaline reaction and imparting a crimson colour to a non-luminous flame. On supersaturating the dilute aqueous solution with hydrochloric acid a bulky white precipitate

is obtained, which is soluble in boiling water, from which it crystallises on cooling; also soluble in ether; and producing an intense violet colour with ferric salts.

Uses.—It is used as a remedy in gout and rheumatism, and is intended to unite the properties of salicylic acid and lithium. It is less irritant to the stomach than salicylic acid.

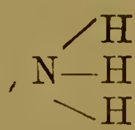
Dose.—20–40 grs. (1·3–2·6 gm.).

Monad Metals.—Group II.

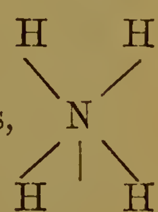
AMMONIUM SALTS. Ammonia. NH_3; 17.

Ammonium salts are well-defined, like those of potassium and sodium, but the base, instead of being a so-called element, is known to be a compound of nitrogen and hydrogen. They are formed by the direct union of ammonia, NH_3, with acids. Thus ammonia and hydrochloric acid unite directly to form ammonium chloride, $NH_3 + HCl = NH_4Cl$. In the case of other members of the metallic group this direct union with the components of the acid does not occur, the metal replacing hydrogen, e.g. $Zn + 2HCl = ZnCl_2 + H_2$. This exception to the general rule may be avoided by regarding the compounds of ammonia with acids as not being formed by the direct union of ammonia with the acids, but by the replacement of hydrogen in a basylous radical ammonium, NH_4.

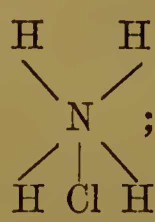
In gaseous **ammonia** the nitrogen may be supposed to be **triad** with its three affinities saturated by hydrogen, thus,



In the radical **ammonium** the nitrogen is supposed to be **pentad**, four of its affinities being saturated by hydrogen, the other being free to unite with an atom of some other element, thus,

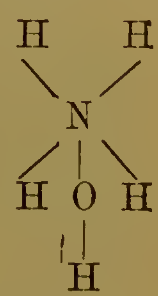


In ammonium chloride this free affinity is saturated by chlorine



;

In liquor ammoniæ this free affinity is saturated by hydroxyl,



The atoms of hydrogen in ammonia or in ammonium can be replaced by organic radicals, and **compound ammonias** are formed. When the organic radical which replaces the hydrogen is of a positive nature, the compounds are termed **amines**, but if it is of a negative nature they are termed **amides**.

Ammonium, NH_4, does not exist in the free state, and whether the double molecule, N_2H_8 or $\begin{matrix} NH_4 \\ | \\ NH_4 \end{matrix}$, exists separately is uncertain.

It has been supposed to form an amalgam with mercury. When mercury, potassium, and sal-ammoniac are mixed, the mercury swells up enormously and forms a pasty amalgam. This may consist of ammonium and mercury, but it soon decomposes into mercury, ammonia, and hydrogen, so that some have supposed it to be nothing more than mercury which has absorbed a certain quantity of gas, as the mercury in this condition yields to pressure in the same way as froth does in other liquids. At all events the salts of ammonium correspond very closely with those of potassium and sodium. In their general reactions they differ, however, in the fact that ammonia is volatile, whereas potassium and sodium are not.

Sources of Ammonium Salts.—Ammonia is formed chiefly by the union of the nitrogen and hydrogen contained in animal or vegetable tissues during the processes of decomposition or destructive distillation. The principal commercial source of ammonium salts is the ammoniacal liquor from gas-works, though some of it is also obtained by the dry distillation of bones in making animal charcoal.

General Reactions of Ammonium Salts.—Like potash and soda, ammonia is not precipitated by most reagents. It is recognised by its volatile alkaline character. It is given off from any of its salts on the addition of caustic potash or soda to them, and is then distinguished by its peculiar smell, and by its volatile alkaline character—turning a piece of red litmus-paper blue and turmeric paper brown, when they are held above the test-glass in which the ammonium salt has been mixed with potash or soda. It also forms white fumes of ammonium chloride when brought near to strong hydrochloric acid.

General Impurities of Ammonium Salts.—As all the salts are obtained from the chloride or sulphate, chlorides or sulphates may be present. Iron may be present, as the chloride is usually sublimed in an iron pot, and, if the heat employed be too great, some ferric chloride sublimes along with the ammonium chloride and gives it a reddish colour. Some lead may also be present from the leaden domes into which the ammonium chloride is sublimed.

General Tests.—Lead and iron are detected by hydrosulphuric acid, or ammonium sulphide, and iron also by ferrocyanide of potassium. As the gas liquor contains many empyreumatic substances, these may sublime, and they are tested for in carbonate of ammonium (U.S.P.) by solution of permanganate of potassium. The colour of this ought not to alter after standing for five minutes.

PREPARATION OF AMMONIUM SALTS.

Is prepared	From	By
Ammonium Chloride, B. and U.S.P.	Gas liquor . .	Adding hydrochloric acid and subliming in iron pots covered with leaden domes; or by adding sulphuric acid, and subliming the ammonium sulphate with sodium chloride in the same way.
Ammonium Sulphate, U.S.P.	Ditto . .	Adding sulphuric acid and subliming.
Liquor Ammoniæ fortior, B.P.; Aqua Ammoniæ fortior, U.S.P.	Ammonium chloride, or sulphate	Heating with lime, and saturating a quantity of water with the gaseous ammonia (NH_3) given off:— $2NH_4Cl + Ca(OH)_2 = CaCl_2 + 2NH_3 + 2H_2O$.
Liquor Ammoniæ, B.P.; Aqua Ammoniæ, U.S.P.	Ditto . .	Is simply liquor ammoniæ fortior diluted with 2 parts of water.
Ammonium Carbonate, B. and U.S.P.	Ditto . .	Subliming with calcium carbonate.
Ammonium Valerianate, U.S.P.	Ditto . .	Mixing with lime and neutralising valerianic acid with the ammonia given off.
Ammonium Iodide, U.S.P.	Ammonium sulphate	Decomposing by potassium iodide, precipitating potassium sulphate by alcohol, filtering, and evaporating.
Ammonium Bromide, B. and U.S.P.	Ditto .	Same process as for iodide, substituting bromide for iodide of potassium. Or by neutralising hydrobromic acid with ammonia.
Liquor Ammonii Acetatis, B. and U.S.P.[1]	Ammonium carbonate	Neutralising with acetic acid.
Spiritus Ammoniæ Aromaticus, B. and U.S.P.	Ammonium carbonate and liquor ammoniæ	Distilling with volatile oil of nutmeg, oil of lemon, rectified spirit, and water, B.P. Oil of lemon, of lavender flowers, and of pimenta are the flavouring agents, U.S.P.
Liquor Ammonii Citratis Fortior, B.P.	Liquor ammoniæ fortior	Neutralising with citric acid. It would be better prepared by neutralising ammonium carbonate with citric acid.
Liquor Ammoniæ Citratis, B.P.	Liquor ammonii citratis	By diluting with water five times.
Ammonium Phosphate, B. and U.S.P.	Liquor ammoniæ .	Neutralising with phosphoric acid.
Ammonium Sulphide	Ditto .	Saturating with hydrogen sulphide.
Ammonium Nitrate, B. and U.S.P.	Liquor ammoniæ or carbonate	Neutralising with dilute nitric acid, evaporating and fusing.

GENERAL ACTION OF AMMONIUM SALTS.—This has already been described, as well as the modifications induced in it by different acid radicals (p. 602). The tetanus produced by ammonia and ammonium chloride is due to their action on the

[1] Liquor ammonii acetatis fortior, B.P., is made from the carbonate, and liquor ammonii acetatis is prepared by diluting the strong solution with water.

spinal cord, and not on cerebral centres, for it persists, like that of strychnine, after section of the cord. The paralysing action of ammonium chloride on the **muscles** modifies the tetanus, in so far that after the first spasm, irritation applied to the skin does not cause tetanic convulsions, but only a single reflex twitch. This effect is usually ascribed to the paralysing action on the **motor nerves**, but it seems really to be due to an affection of the muscles (Fig. 167), as well as to a disturbance of the relation between the muscle and motor nerve. Amylamine, which is a compound ammonia, has a paralysing action on muscle similar to ammonia, as shown in Fig. 168. When a muscle has been poisoned by some ammonium salt, a single stimulation applied to

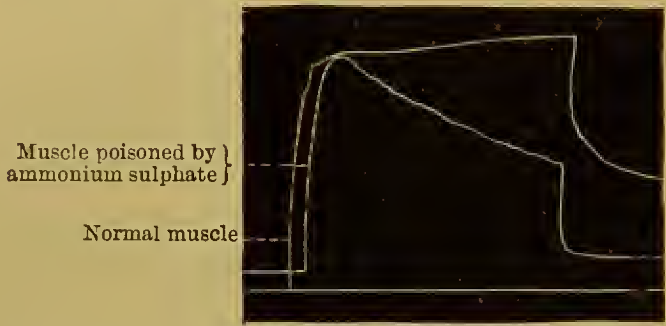


FIG. 167.—Tetanus-tracing to show the paralysing action of ammonium sulphate on muscle. The first contraction of the poisoned muscle is nearly as great as that of the unpoisoned one, but it soon becomes exhausted, and the curve rapidly falls during the continuance of the stimulation, while that of the normal muscle rather rises.

the nerve causes a strong contraction like that of an unpoisoned muscle; but a second stimulus has sometimes little or no action, and when the muscle is stimulated directly it soon becomes exhausted. Ammonia is a powerful muscular irritant, causing contraction and subsequent rigor mortis when applied directly to voluntary muscle.

FIG. 168.—Tetanus-tracing to show the paralysing action of amylamine on muscle. Cf. Fig. 167.

Ammonium salts are said to increase the secretion of the **mucous glands** of the **bronchi** and of the **intestine**, as well as that of the **sweat-glands** and of the **kidneys**. Ammonia appears to be converted almost entirely into **urea** in the blood of mammals, but in birds it is converted into uric acid.[1]

[1] Schröder, quoted by Kmerin, *Ztschr. f. Biol.*, xxi. p. 76.

It increases the formation of **glycogen** in the liver.[1]

Neither ammonia, nor its carbonate, nor its salts with organic acids diminish, but rather increase the acidity of the urine, and in this ammonia differs from potash, soda, and lithia.

Ammonii Chloridum, B. and U.S.P. CHLORIDE OF AMMONIUM. NH_4Cl; 53·4.

CHARACTERS.—In colourless, inodorous, translucent, fibrous masses, tough, and difficult to powder.

SOLUBILITY.—It is soluble in water and in rectified spirit.

REACTIONS.—When heated it volatilises without decomposition, and leaves no residue. Its solution in water gives the reactions of ammonia (p. 634) and a chloride (p. 594).

PREPARATION. U.S.P.

		DOSE.
Trochisci Ammonii Chloridi.	2 grains in each	1 every hour or two.

DOSE.—5 to 20 grains.

ACTION AND USES.—Cold is produced during the process of solution in water of ammonium chloride, and so its solution has been used **locally** in headache, inflammation of the brain, mania, and apoplexy. It has been employed as a lotion to remove ecchymoses, to prevent discoloration in bruises and sprains, and to allay itching in prurigo. It has been applied locally as a dressing in abscess of the mamma, and to remove glandular enlargements. As a gargle, it has been used to cause contraction of the enlarged flabby uvula, and to relieve the cough which the tickling of the pharynx by the uvula often causes.

A **small dose** of 5 to 7 grs. of ammonium chloride has no effect, but if taken frequently it causes discomfort and heat in the stomach, slight headache, diuresis, and an increased secretion of mucus from the intestine, although the stools are not more numerous.

Large doses given to animals often cause pain and excitement, then collapse (no diarrhœa), convulsions, and death. The stomach is congested, the mucous membrane swollen, and the epithelial cells easily separated.

The same symptoms are produced when ammonium chloride is applied to a wound, and the same *post-mortem* appearances are seen in the stomach.

It thus seems to have a special action on the **gastric mucous membrane**. It is used in Germany in cases which are usually supposed to be due to a catarrhal state of the stomach—viz. when there is loss of appetite, sickness, bad taste in the mouth, fulness in the stomach, and flatulence, with a coated tongue, and along with these bronchial catarrh without fever. Ammonium

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[1] Rohmann, *Centralblatt f. klin. Med.*, No. 36, 1884.

carbonate is preferred when there is much cough or the person is weak.

It is also used alone in **bronchial catarrh**, when this has either come on without fever, or the feverish symptoms have passed off. It is supposed to have the power of increasing the secretion of mucus in the bronchi as well as in the intestine, and it is therefore not given when the expectoration is profuse, but only when it is scanty and difficult to bring up.

It has been given to relieve the vomiting and heartburn occurring in cancer of the stomach. It is said to have a powerful action on the **liver** (p. 636), and has been strongly recommended in chronic congestion and hepatic abscess, as well as in dropsy depending upon hepatic disease. For its alterative action it has been given in muscular rheumatism, rheumatic pains, and neuralgia. In neuralgia it should be given in half-drachm doses several times a day; but if the pain is not relieved after four or five doses have been given, it may be discontinued. It is also useful in neuralgic headaches.

Liquor Ammoniæ Fortior, B.P.; Aqua Ammoniæ Fortior, U.S.P. STRONG SOLUTION OF AMMONIA, B.P.; STRONGER WATER OF AMMONIA, U.S.P.

CHARACTERS.—A colourless liquid, with a characteristic and very pungent odour, and strong alkaline reaction. Specific gravity 0·891.

PREPARATIONS IN WHICH STRONG SOLUTION OF AMMONIA IS USED.

B.P.	U.S.P.
Ammonii Phosphas.	Spiritus Ammoniæ.
Linimentum Camphoræ Compositum (p. 516).	
Liquor Ammoniæ.	
„ Ammonii Citratis Fortior.	
Spiritus Ammoniæ Aromaticus.	
„ „ **Fœtidus.**	
Tinctura Opii Ammoniata.	

ACTION AND USES.—When applied to the nose, the vapour of strong ammonia acts as a powerful irritant. It **stimulates** the nasal branches of the fifth nerve, and thus reflexly excites the vaso-motor centre and raises the blood-pressure. It thus tends to prevent or to remove conditions of shock and syncope. When applied for too long a time, or in too concentrated a form, it may produce inflammation of the mucous membrane and respiratory passages. Applied to the skin it quickly evaporates, and has but a slight **rubefacient** effect, but when its evaporation is prevented it passes through the epidermis and acts as a powerful **vesicant**. When swallowed in large quantities, and undiluted, it may produce gastro-enteritis, but on account of the vapour gaining access to the air-passages and causing immediate suffocation, it may cause death in a few minutes. Along with the gastro-enteritis there may be comatose symptoms due to the

action of the drug itself on the **brain** after absorption, and in this it differs from poisoning by caustic potash or soda. It stimulates the **circulation** reflexly through the nerves of the stomach, and after its absorption stimulates both the **respiration** and circulation by its direct action upon the circulatory and respiratory nerve-centres.

USES.—**Inhalation** of its fumes is used to prevent drowsiness or fainting, or to recover persons from a faint, or from shock, or from the narcosis produced by opium, syncope, or the depression caused by vascular sedatives. It should not be applied for too long a time, lest bronchitis be induced. It is sometimes employed in a milder form to cut short nasal catarrh, to lessen pain in the nose and forehead, and diminish the expectoration in chronic bronchitis. It is used as a **counter-irritant** to the skin in rheumatic pains, stiffened rheumatic joints, and bronchitis. As a **vesicant** it may be employed where the use of cantharides is objectionable. A pledget of lint, somewhat larger than the blister desired, is moistened with ammonia, covered with a watch-glass, and applied to the skin until a red ring forms round the glass. The pledget is then removed and a poultice applied. The poison of nettles and insects is frequently of an acid character, and ammonia rubbed over the part stung will lessen the pain and swelling. The injection of ten drops of strong liquor ammoniæ, diluted with three parts of water, into the veins, has been recommended in cases of **snake-bite**. It may be useful possibly in bites of less poisonous snakes, but is of no utility in bites by the cobra or daboia. It may be given internally, diluted, as a stimulant in cases of syncope, and in the depression, weakness, and faintness to which some women are subject. In these cases the liquor ammoniæ may be employed as a **substitute for alcohol**, and thus the tendency to contract habits of drinking may be counteracted. It may be used, like other alkalis, to stimulate the secretion of gastric juice, and especially where we do not wish to diminish the acidity of the urine or render it alkaline, and also where we wish to stimulate the **nervous system**, as in cases of anæmia and debility, and more especially where the stomach is relaxed and distended with gas. It also stimulates the **intestines**, and aids the expulsion of gas from them. It is therefore very useful in the flatulence and colic of children. It may be employed to lessen the watery discharge from the bowels where this persists after the removal of the irritant which has caused it.

U.S.P. Spiritus Ammoniæ. SPIRIT OF AMMONIA.—An alcoholic solution of ammonia containing 10 per cent. by weight of the gas.

PREPARATION.—By warming strong water of ammonia so as to expel the ammoniacal gas, passing this into cold alcohol, and diluting with alcohol to the necessary strength.

Liquor Ammoniæ, B.P.; Aqua Ammoniæ, U.S.P. SOLUTION OF AMMONIA, B.P.; WATER OF AMMONIA, U.S.P.—Ammoniacal Gas, NH_3; 17; dissolved in water.

PREPARATION.—By mixing 1 part of strong solution of ammonia with 2 of water.

PREPARATIONS.

B.P.	U.S.P.
Linimentum Ammoniæ (p. 516).	Spiritus Ammoniæ Aromaticus. Linimentum Ammoniæ (p. 517).

DOSE.—10 to 30 minims well diluted.

USES.—This may be used as a local application in a similar manner to the liquor ammoniæ fortior, except that it has not the same powerful vesicant action. It may be given internally for similar purposes. When mixed in the proportion of two ounces of liquor ammoniæ with two ounces of common salt and three drachms of camphorated spirit of wine to thirty-two ounces of water, it forms Raspail's sedative solution, for the treatment of headaches occurring at the menopause, or due to uterine derangement.

Ammonii Carbonas, B. and U.S.P. CARBONATE OF AMMONIUM, $N_3H_{11}C_2O_5$, B.P. $NH_4HCO_3NH_4NH_2CO_2$; 157, U.S.P.

A volatile and pungent ammoniacal salt, produced by submitting a mixture of sulphate or chloride of ammonium and carbonate of calcium to sublimation. It consists of a mixture of acid carbonate of ammonium (NH_4HCO_3), and carbamate of ammonium ($NH_4NH_2CO_2$).

CHARACTERS.—In translucent crystalline masses, with a strong ammoniacal odour, and alkaline reaction.

SOLUBILITY.—Soluble in cold water, more sparingly in spirit.

REACTIONS.—It volatilises entirely when heated, and is readily dissolved by acids with effervescence.

$$\left.\begin{array}{l}\text{20 grains of Carbonate}\\ \text{of Ammonium}\end{array}\right\}\text{neutralise}\left\{\begin{array}{l}23\tfrac{1}{2}\text{ grains Citric Acid.}\\ 25\tfrac{1}{2}\text{ grains Tartaric Acid.}\end{array}\right.$$

DOSE.—3 to 10 grains as stimulant and expectorant, 30 grains as emetic.

PREPARATIONS IN WHICH CARBONATE OF AMMONIUM IS USED.

B.P.	U.S.P.
Liquor Ammonii Acetatis. **Spiritus Ammoniæ Aromaticus.**	Spiritus Ammoniæ Aromaticus.

USES.—Carbonate of ammonium may be used as an inhalation, and may be given internally, for similar purposes to liquor ammoniæ.

It is an **emetic**, and may be employed in cases of bronchitis, where the bronchial tubes are choked with mucus, and the patient's circulation is weak. In smaller doses it stimulates the secretion of gastric juice, and may be used in atonic dyspepsia,

flatulence, and colic to relieve sinking and depression, and as a substitute for alcoholic stimulants. When employed for this latter purpose, five to ten grains may be given along with ten minims of tincture of capsicum in an ounce of bitter infusion, to be taken whenever the feeling of sinking comes on, or the craving for alcoholic stimulants is experienced.

From its power of stimulating the respiratory centre, it is employed as a stimulating **expectorant** in chronic bronchitis, in the broncho-pneumonia of children, and in asthma depending on cardiac disease. It is also given in measles, and has been recommended as almost a specific in scarlet fever, in doses of three to five grains, every one, two, or three hours, according to the severity of the case, no acid drinks or fruits being allowed to the patient at the time.

Carbonate of ammonium has been supposed to have the power of preventing iodism, when given along with iodide of potassium.

Spiritus Ammoniæ Aromaticus, B. and U.S.P. AROMATIC SPIRIT OF AMMONIA (SAL VOLATILE).—It consists of carbonate of ammonium, and strong solution of ammonia diluted with alcohol and water. It is flavoured with volatile oil of nutmeg and oil of lemon in the B.P., and with oil of lemon, oil of lavender flowers, and oil of pimenta, in the U.S.P.

DOSE.—20 to 60 minims in water.

PREPARATIONS.

Tinctura Guaiaci Ammoniata. B. and U.S.P.
„ **Valerianæ Ammoniata.** „ „

USES.—It is very commonly taken to relieve feelings of faintness and depression, and is much safer than alcohol, which might otherwise be employed. It may be used also for other purposes instead of carbonate of ammonium, to which it has a similar action.

B.P. Liquor Ammonii Acetatis Fortior. STRONG SOLUTION OF ACETATE OF AMMONIUM. Sp. gr. 1·073.

DOSE.—25 to 75 minims.

Liquor Ammonii Acetatis, B. and U.S.P. SOLUTION OF ACETATE OF AMMONIUM.—Acetate of Ammonium, $NH_4C_2H_3O_2$, dissolved in water.

DOSE.—2 to 6 fluid drachms.

USES.—It is used as an eyewash, and as a lotion to inflamed parts. When given internally it acts as a **diaphoretic**, if the body be kept warm, or as a **diuretic** if it be cool. As a diaphoretic it is given when the skin is hot and dry, and is very frequently used, especially combined with spirit of nitrous ether, whenever a feverish condition is present, whether its cause be

known or not. It is especially used in the exanthemata, in influenza and catarrh.

B.P. Liquor Ammonii Citratis Fortior. STRONG SOLUTION OF CITRATE OF AMMONIUM. Neutral. Sp. gr. 1·209.

DOSE.—½ to 1½ fl. dr.

B.P. Liquor Ammonii Citratis. SOLUTION OF CITRATE OF AMMONIUM.—Citrate of Ammonium, or $(NH_4)_3.C_6H_5O_7$, dissolved in water.

DOSE.—2 to 6 fluid drachms.

USES.—Like the solution of the acetate, but more agreeable.

B.P., Appendix, Oxalate of Ammonium $(NH_4)_2C_2O_4.H_2O$.

PROPERTIES.—Colourless prismatic crystals, no smell.

USES.—Used to test for calcium, and to separate it from magnesium.

Ammonii Phosphas, B. and U.S.P. PHOSPHATE OF AMMONIUM. $(NH_4)_2HPO_4$; 132.

CHARACTERS.—In transparent colourless prisms.

SOLUBILITY.—Soluble in water, insoluble in rectified spirit.

REACTIONS.—The aqueous solution gives the reactions of ammonia, and of a phosphate (p. 595).

DOSE.—5 to 20 grs. freely diluted.

USES.—It has been used as a remedy in cases of gout, in order to eliminate urate of sodium from the system, the theory of its action being that it decomposes the insoluble urate of sodium, converting it into soluble urate of ammonium and phosphate of sodium.

Ammonii Bromidum.—*Vide* p. 556.

Ammonii Iodidum.—*Vide* p. 664.

Ammonii Nitras, B. and U.S.P. NITRATE OF AMMONIUM. NH_4NO_3 ; 80.

CHARACTERS.—Colourless crystals, generally in the form of long thin rhombic prisms, or in fused masses somewhat deliquescent, odourless, having a sharp bitter taste and a neutral reaction.

REACTIONS.—When gradually heated, the salt melts at 165° to 168° C. (329° to 331° F.), and at about 185° C. (365° F.) it is decomposed into nitrous oxide gas and water, leaving no residue. The aqueous solution of the salt, when heated with potassa, evolves vapour of ammonia. On heating the salt with sulphuric acid, it emits nitrous vapours.

USE.—It is only used for the preparation of nitrous oxide.

U.S.P. Ammonii Sulphas. SULPHATE OF AMMONIUM. $(NH_4)_2SO_4$; 132.

CHARACTERS.—Colourless transparent rhombic prisms, permanent in the air, odourless, having a sharp saline taste, and a neutral reaction.

Uses.—It is not used internally, but is only employed for the preparation of other salts of ammonium, of ammonium alum (B.P.) and sulphate of iron and ammonium (U.S.P.).

U.S.P. Ammonii Valerianas. Valerianate of Ammonium. $NH_4C_5H_9O_2$; 119.

Characters.—Colourless or white quadrangular plates, deliquescent in moist air, having the odour of valerianic acid, a sharp and sweetish taste, and a neutral reaction.

Solubility.—Very soluble in water and in alcohol.

Reactions.—When heated the salt fuses, gives off vapour of ammonia, and of valerianic acid, and is finally dissipated without leaving a residue.

Dose.—2 to 8 grs. (0·13 to 0·52 gm.).

Use.—It is chiefly used, like valerian, in cases of hysteria.

Ammonii Benzoas, B. and U.S.P. Benzoate of Ammonium, $NH_4C_7H_5O_2$; 139.

Characters.—Thin white four-sided laminar crystals, permanent in the air, having a slight odour of benzoic acid, a saline, bitter, afterwards slightly acrid taste, and a neutral reaction.

Reactions.—When strongly heated the salt melts, emits vapours having the odour of ammonia and of benzoic acid, and is finally wholly dissipated.

Uses.—It is used as a **diuretic**, and to render the urine acid where there is a tendency to phosphatic deposits.

B.P. Sulphide of Ammonium.—$(NH_4)_2S$. Test Solution.

Properties.—Greenish-yellow transparent liquid, with a disagreeable pungent odour. S.G. 0·999.

Preparation.—Saturate a solution of ammonia by sulphuretted hydrogen.

Dose.—3 minims, cautiously increased.

Actions.—In small doses it increases secretion, especially of bronchi and skin, and is thus used as a sudorific and expectorant in chronic skin-diseases, rheumatism, and bronchitis; in large doses it causes giddiness, drowsiness, faintness, and nausea. Little given.

It is chiefly used as a test.

CHAPTER XXV.

METALS—(*continued*).

Class II.—DYAD METALS.

Group I.—METALS OF THE ALKALINE EARTHS.

Calcium, *Strontium*, Barium.

Appendix.—METALS OF THE EARTHS.

Aluminium, (? triad) *Beryllium* (dyad), *Zirconium* (tetrad), *Niobium* (tetrad), Cerium, *Lanthanum*, *Didymium*, *Yttrium*, *Erbium* (triads).

Group II.—MAGNESIUM.

Group III.—COPPER, ZINC, SILVER, *Cadmium*.

Group IV.—MERCURY..

This large class contains a number of metals which have widely different characters and reactions. Yet it will be seen from the following table that the successive addition of four reagents divides the metals tolerably nearly into those groups which agree in their physiological action. In some respects Groups I. and II. of Class 2 are perhaps more closely connected with the alkaline metals than with the heavy metals.

REACTIONS OF THE METALS IN CLASS II.

	Hydrochloric Acid	Sulphuretted Hydrogen	Ammonium Sulphide	Ammonium Carbonate	Ammonia and Sodium Phosphate
GROUP I.					
Calcium	No precipitate.	No precipitate.	No precipitate.	White precipitate.	
Strontium	Do.	Do.	Do.	Do.	
Barium	Do.	Do.	Do.	Do.	
(APPENDIX.)					
Aluminium	Do.	Do.	White (Hydrate)		
All other earthy metals	Do.	Do.	Do.		
GROUP II.					
Magnesium...	Do.	Do.	No precipitate.	No precipitate.	White ppt. (phosphate).
GROUP III.					
Zinc..........	Do.	Do.	White (sulphide)		
Copper	Do.	Black ppt.			
Cadmium	Do.	Yellow ppt.			
Silver.........	White curdy ppt. soluble in ammonia.	Black ppt.			
GROUP IV.					
Mercury as sub-salt	White ppt.	Black ppt.			
Do. as persalt..	No precipitate	Do.			

It must be borne in mind that the above reagents are used successively, and each remains in the solution. Thus when ammonium sulphide is added, part of it is decomposed by the hydrochloric acid and ammonium chloride is formed. It is on account of the presence of the ammonium chloride in the liquid that magnesium is not precipitated by the ammonium sulphide, while aluminium is.

Class II. GROUP I.

GENERAL ACTION.—In regard to the action on the nervous system of the chlorides of calcium, strontium, barium, beryllium, didymium, erbium, and lanthanum, these substances fall into two groups—

(*a*) Containing beryllium, calcium, strontium, and barium ;
(*b*) Containing yttrium, didymium, erbium, and lanthanum.

Group (a) has a tendency to increase reflex action, as evidenced by spasm or tremor in the frog.

With group (b) reflex action in the cord appears to be little affected, but its members appear to have a tendency to paralyse motor centres of the brain in the frog.

Group (*a*) all paralyse motor nerves to some extent. Lanthanum has also a slight paralysing action, but the other members of the group (*b*) have not, agreeing in this respect with sodium and rubidium, and differing from all the others.

In regard to their action on muscle these substances cannot be divided into sub-groups. Their action on muscle has been already described (p. 135).

The lethal activity, on frogs, of the chlorides of the alkalies and earths is not in proportion to their atomic weight. It is as follows, potassium being most powerful, and calcium least powerful:—potassium, beryllium, rubidium, barium, ammonium, cæsium, lithium, lanthanum, didymium, erbium, strontium, yttrium, sodium, calcium (*vide* p. 29).

Barium causes contraction of the ventricle of the frog's heart in much the same way as veratrine, and by its local action on the walls of the vessels causes them to contract. When injected into the circulation it causes enormous rise of blood-pressure at first, followed by stoppage of the heart and consequent fall of pressure. It causes contraction also of the involuntary fibres of the bladder and intestine, so that the lumen of the latter may be almost completely obliterated. The symptoms of poisoning in mammals are probably due to its action on the involuntary muscles of the intestines, heart, and vessels, on the voluntary muscles, and on the nervous system. They are vomiting, colic, diarrhœa, muscular weakness and cramp, ringing in the ears, tightness over the heart, and general convulsions. Injection of sulphate of sodium into the veins appears to counteract the effect of barium,[1] and the simultaneous injection of potassium salts will prevent death from an otherwise lethal dose of barium.[2] The action of barium on muscles and on the heart is abolished by heat in the same way as that of veratrine (p. 128), and the inhabitants of southern climates tolerate much larger doses of barium than those of northern.[3]

Metals of the Alkaline Earths.

Calcium, *Strontium*, Barium.

The only one of these whose preparations are used internally is calcium. At present barium is only used as a test, though possibly it may yet prove useful in muscular tremor (p. 134).

CALCIUM. Ca; 40, or 39·9.

Sources of Calcium-salts.—The chief source is the carbonate found native as chalk or limestone.

General Test of Calcium-salts.—The addition of ammonium oxalate to calcium salts causes a white precipitate of calcium oxalate, which is very sparingly soluble in water. It is soluble in hydrochloric, but insoluble in acetic acid.

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[1] Hermann, *Lehrbuch d. experimentel. Toxicologie*, p. 191.
[2] Brunton and Cash, *Centralblatt für d. med. Wissenschaften*, 1884, p. 545.
[3] Lisfranc, quoted by Lewin, *Nebenwirkungen d. Arzneimittel*, p. 74.

GENERAL PREPARATION OF SALTS OF CALCIUM.

Is prepared	From	By
Creta præparata, B. and U.S.P.	Chalk . . .	The process of elutriation, which consists in stirring with water, pouring off the liquid containing fine particles in suspension, and allowing them to subside.
Calx (quicklime), B. and U.S.P.	Chalk or limestone .	Calcining; $CaCO_3 = CaO + CO_2$.
Calcii hydras (slaked lime), B.P.	Quicklime . .	Slaking with water.
Calcii chloridum, B. and U.S.P.	Limestone or chalk (Carbonate) . .	Neutralising with hydrochloric acid; $CaCO_3 + 2HCl = CaCl_2 + H_2O + CO_2$.
Calcii carbonas præcipitata, B. and U.S.P.	Calcium chloride .	Precipitating with excess of carbonate of sodium; $CaCl_2 + Na_2CO_3 = CaCO_3 + 2NaCl$.
Calx chlorata (chlorinated lime), B. and U.S.P.	Slaked lime . .	Exposing lime to chlorine gas until saturated: thus is formed chlorinated lime, consisting of a mixture of calcium chloride and calcium hypochlorite.
Calcii hypophosphis, B. and U.S.P.	Lime and phosphorus	Heating together with water; removing excess of lime by CO_2, and evaporating.
Calcii phosphas, B. and U.S.P.	Bone ash . .	Dissolving in diluted hydrochloric acid, precipitating with ammonia, and drying.

GENERAL IMPURITIES.—The chief impurities are aluminium and magnesium.

TESTS.—These are usually detected by converting the calcium-salt into chloride by hydrochloric acid, and evaporating to dryness so as to drive off all excess of acid. The residue is re-dissolved in water and the tests applied to the solution. On the addition of saccharated solution of lime, aluminium and magnesium will be precipitated. The B.P. states that only a very scanty precipitate should occur, showing that only traces of magnesium and aluminium are present. The test used in the U.S.P. to detect aluminium is water of ammonia; and to detect magnesium, water of ammonia and phosphate of sodium. These reagents should not give more than a faint turbidity with dilute solutions of calcium salts.

B.P. Marmor Album. WHITE MARBLE. $CaCO_3$.
Hard white crystalline native carbonate of calcium, in masses. Used in producing carbonic acid gas.

B.P. Creta. CHALK. $CaCO_3$. Native friable carbonate of calcium. Used in producing carbonic acid gas.

PREPARATION.

Creta Præparata.

Calx, B. and U.S.P. LIME. CaO; 56.
An alkaline earth, oxide of calcium, CaO, with some impurities, obtained by calcining chalk or limestone so as to expel carbonic acid.

CHARACTERS.—In compact masses of a whitish colour, which readily absorb water, and which, when rather less than their weight of water is added, crack and fall into powder with the development of much heat.

TESTS.—The powder obtained by the process of slaking, when agitated with distilled water, gives, after filtration, a clear solution which has an alkaline reaction, and is shown by the appropriate tests to contain calcium and only traces of aluminium and magnesium.

PREPARATIONS.

B.P.	U.S.P.
Calcii hydras.	Liquor Calcis.
	Potassa cum Calce (p. 608).
	Syrupus Calcis.

B.P. Calcii Hydras. SLAKED LIME.

Hydrate of lime, $Ca(HO)_2$; 74; with some impurities, recently prepared by pouring 1 pint of water over 2 lbs. of lime in a metal pot.

SOLUBILITY.—It dissolves in water, but only sparingly, 11 grs. being dissolved by a pint of water at 60° F.; and, contrary to the usual rule, its solubility is increased by cooling the water, and diminished by heating it.

Its solubility is greatly increased by the addition of sugar, as in the Liquor Calcis Saccharatus, B.P., or Syrupus Calcis, U.S.P.

PREPARATIONS.

	DOSE.
Liquor Calcis.	1–4 fl. oz.
Liquor Calcis Saccharatus.	15–60 min.

Liquor Calcis Saccharatus, B.P.; Syrupus Calcis, U.S.P. SACCHARATED SOLUTION OF LIME, B.P.; SYRUP OF LIME, U.S.P.

PREPARATION.—B.P. Like lime-water, mixing 1 ounce of lime with 2 of sugar and using them instead of 2 of lime. This mixture contains 7·11 grains of lime in 1 fluid ounce. U.S.P. Mixing lime (5) and sugar (30) with boiling water (50); diluting with an equal volume of water, filtering, and evaporating to 100 parts.

DOSE.—15 to 60 minims.

Liquor Calcis, B. and U.S.P. SOLUTION OF LIME. LIME WATER.

PREPARATION.—B.P. By shaking 2 ounces of slaked lime with 1 gallon of distilled water in a stoppered bottle well for two or three minutes. After twelve hours the excess of lime will have subsided, and the clear solution may be drawn off with a syphon as it is required for use, or transferred to a green glass bottle furnished with a well-ground stopper. In the U.S.P. the lime is first washed with ordinary water and afterwards stirred well with distilled water.

It is a saturated solution, and contains a little over half a grain to an ounce.

DOSE.—1–4 fl. oz.

PREPARATIONS.

B.P.	U.S.P.
Linimentum Calcis (p. 516).	Linimentum Calcis (p. 517).
Argenti Oxidum.	
Lotio Hydrargyri Flava.	
,, ,, Nigra.	

USES.—When applied to the surface either of the skin or of a mucous membrane from which a watery discharge is issuing, lime seems to act as a slight **astringent**, possibly because it combines with the albumen.

Lime-water is therefore sometimes used as a lotion for cracked nipples and as a dressing to eczematous surfaces, where it eases the smarting and tingling. It is often mixed with oil, as in linimentum calcis, or glycerine for this purpose. The efficacy of the liniment is much increased by the addition of minute quantities of carbolic acid.

Linimentum Calcis—better known, perhaps, under the name of Carron oil—is used as an application to burns and scalds. It derives its name of Carron oil from its being so extensively used by the workmen in the foundries at Carron.

It was formerly made with linseed oil, and this preparation is less fluid, and is often preferable to that made with olive or cotton-seed oil. It is useful not only in burns and scalds, but as a dressing to the face in small-pox, and in some cases of eczema affecting a large extent of skin.

Lime-water is also used as an injection to lessen discharges from the ears, urethra, vagina or vulva, in otorrhœa, gleet, and leucorrhœa, while active inflammation is still present, and as an enema to destroy ascarides in the rectum. It may also be used as a wash to the mouth in ulceration. In croup it has been recommended as a solvent for the false membrane. It is either applied as spray or by a camel's-hair pencil. When taken into the stomach it will act as an **antacid.** It is especially useful in preventing vomiting, and a mixture of milk and lime-water will often be retained by the stomach and digested when no other food can be borne. In children suffering from chronic vomiting and diarrhœa, where the milk is vomited in hard lumps instead of small flakes, lime-water proves very useful.

In typhoid fever it tends to prevent milk from forming hard undigested lumps which may irritate the intestine, while it has at the same time an astringent action.

It is very useful as an **astringent** in diarrhœa, more especially in slight cases of diarrhœa in children. When the child is at the breast about one teaspoonful of lime-water mixed with an equal quantity of milk should be given to it every three hours, and when it is brought up by hand the lime-water is just mixed with the milk which the child ordinarily takes. It has been used in diarrhœa in adults depending on ulceration of the intestine, with the view of healing the ulcers by combining with the albumen on their surface and thus forming a coating over them, but it is not so efficient as other remedies for this purpose.

Only a small quantity is absorbed by the intestine and passes into the blood; yet, after it has been used for a little while, the urine becomes alkaline from the lime being excreted by the kidneys. Lime-water has been used in cases of stone, and with considerable benefit. It has been supposed to dissolve stones in the bladder; but the good effects which result from its use are probably not due to this cause, which is still problematical.

They are most probably produced by the lime lessening the irritating qualities of the urine, and at the same time acting as an astringent on the walls of the bladder and rendering it less irritable.

Liquor Calcis Saccharatus, B.P., or Syrupus Calcis, U.S.P., may be given in milk instead of liquor calcis, when it is desired simply to get the effect of the lime and it is unadvisable to dilute the milk, as admixture with liquor calcis would necessarily do. It has been used also in acute rheumatism.

Creta Præparata, B. and U.S.P. PREPARED CHALK.

PROPERTIES.—It is a white powder, or in small lumps which break into powder readily on pressure. It has no taste or smell.

PREPARATION.—Prepared chalk is simply chalk freed from sand and other impurities by elutriation (p. 647).

SOLUBILITY.—It is insoluble in water, but it dissolves in acids such as acetic acid.

REACTIONS.—While doing so it effervesces strongly, showing that it is a carbonate, and the solution gives the reactions of calcium (p. 646).

IMPURITIES.—Silica, barium, strontium, magnesium, iron.

TEST.—It should dissolve without leaving any residue in hydrochloric acid (absence of silica), B.P. The solution in acetic acid should give no precipitate with test solution of sulphate of calcium (absence of strontium and barium), and the tests for magnesium and iron should not indicate more than traces of these substances, U.S.P.

DOSE.—10 to 60 gr.

OFFICINAL PREPARATIONS.

B.P.	DOSE.
Mistura Cretæ. Chalk mixture. Chalk (1) suspended in cinnamon water (30) by means of gum (1) and sweetened with syrup (2)	1–2 fl. oz.
Pulvis Cretæ Aromaticus. Aromatic powder of chalk. Cinnamon (8), cardamoms (2), cloves (3), nutmeg (6), saffron (6), sugar (50), chalk (22)	10–60 gr.
Pulvis Cretæ Aromaticus cum Opio. Aromatic powder of chalk thoroughly mixed with powdered opium. 1 part of opium in 40	10–40 gr.
U.S.P.	
Mistura Cretæ. Chalk mixture. Compound chalk powder (20), cinnamon water (40), water (40)	½–2 fl. oz.
Pulvis Cretæ Compositus. Compound chalk powder. Prepared chalk (30), powdered acacia (20), sugar (50)	8-60 gr. (½–4 gm.).
Trochisci Cretæ. Chalk lozenges. 4 grains in each	*Ad lib.*

Chalk is also contained in Hydrargyrum cum Creta, B. and U.S.P.

ACTION.—Carbonate of calcium or chalk possesses the **astringent** and **antacid** powers of lime itself, and is without its irritating qualities. It can therefore be given in much larger doses, and so chalk is used, instead of liquor calcis, in the diarrhœa of adults accompanied by acidity.

USES.—Chalk may be used as a dusting powder to the skin in excoriations, burns, and ulcers. It forms a useful tooth-powder. Internally it serves to arrest diarrhœa, and is often given, whatever be the cause of the diarrhœa; but when the disease depends upon

some irritating substance in the intestine, the irritant should be removed by a dose of castor oil previous to the administration of the chalk. In the form of whiting, chalk forms a useful antidote in cases of poisoning by acids, and especially by oxalic acid.

Calcii Chloridum, B. and U.S.P. CHLORIDE OF CALCIUM. $CaCl_2$; 110·8.

CHARACTERS.—Colourless, slightly translucent, hard and friable masses, very deliquescent, odourless, having a hot, sharp, saline taste, and a neutral or faintly alkaline reaction.

SOLUBILITY.—Soluble in 1·5 parts of water, and in 8 parts of alcohol at 15° C. (59° F.).

REACTIONS.—The aqueous solution yields the reactions of calcium (p. 646) and of a chloride (p. 594).

DOSE.—1 to 3 grains for children, and 10 to 20 for adults in syrup. May be given in milk after meals.

OFFICINAL PREPARATION.

B.P.

Liquor Calcii Chloridi. SOLUTION OF CHLORIDE OF CALCIUM. Calcium chloride 1, water 5 parts. DOSE.—15–50 minims. It is used as a test for tartrates, citrates, and oxalates.

USES.—Chloride of calcium was in much greater use formerly than at present. It was strongly recommended by Dr. Warburton Begbie for cases of strumous enlargement of the cervical glands, for strumous children with hectic, diarrhœa, and loss of appetite, and for the chronic diarrhœa of children. It reduced the glandular swelling and improved the general health, increasing the appetite: to do good, however, the drug must be taken for months and even as long as two years.[1] It has, however, fallen almost into disuse, and is now practically replaced by cod-liver oil and other tonics.

It has a great affinity for water, and is used to remove water from other substances in pharmacy, e.g. in the preparation of absolute alcohol or ether.

Calcii Carbonas Præcipitata, B.P.; Calcii Carbonas Præcipitatus, U.S.P. PRECIPITATED CARBONATE OF CALCIUM. $CaCO_3$; 100.

CHARACTERS.—A very fine white impalpable powder, permanent in the air, odourless and tasteless.

SOLUBILITY.—It is insoluble in water or alcohol.

REACTIONS.—Wholly soluble in hydrochloric, nitric, or acetic acid, with copious effervescence. A neutral solution of the salt in acetic acid yields the reactions of calcium.

USE.—It may be used as an **astringent** in the same way as chalk.

Calcii Bromidum, U.S.P.—*Vide* p. 556.

[1] Warburton Begbie's Works; *New Sydon. Soc.*

Calcii Phosphas, B.P.; Calcii Phosphas Præcipitatus, U.S.P. PHOSPHATE OF CALCIUM, B.P.; PRECIPITATED PHOSPHATE OF CALCIUM, U.S.P. $Ca_3(PO_4)_2$; 310 (*Synonym*, PHOSPHATE OF LIME).

CHARACTERS.—A light, white, amorphous powder, permanent in the air, odourless, tasteless.

SOLUBILITY.—It is insoluble in water or alcohol.

IMPURITIES AND TESTS.—Wholly soluble in nitric or hydrochloric acid without effervescence (absence of carbonate). A solution of the salt in diluted nitric acid, after being mixed with an excess of acetate of sodium, yields a white precipitate with test solution of oxalate of ammonium (calcium), and a lemon-yellow precipitate with test solution of ammonio-nitrate of silver (phosphate).

DOSE.—1–20 grains. A simple way of giving it is to mix it with the salt used at meals.

OFFICINAL PREPARATIONS.

B.P.	U.S.P.	DOSE.
It is contained in **Pulvis Antimonialis.**	Syrupus Calcii Lactophosphatis.	1–4 fl. dr. (7·5–15 cc.).

U.S.P. Syrupus Calcii Lactophosphatis. SYRUP OF LACTOPHOSPHATE OF LIME. Made by dissolving freshly-precipitated phosphate in lactic acid, and mixing with orange-flower water and sugar (22 parts phosphate in 1,000).

ACTION.—Phosphate of calcium is an important constituent of the body, and occurs in considerable quantity wherever active cell-growth, either normal or pathological, is going on. It forms a large proportion of bones, and Chossat found that when animals were fed on food containing no lime-salts, the bones were soft. During pregnancy, fractures unite slowly, and Milne-Edwards found that when animals were supplied with abundance of phosphate of calcium fractures united more quickly.

It has been supposed that the constant use of fine flour tends to cause premature decay of the teeth, owing to the want of sufficient proportion of lime-salts. The decay of the teeth amongst Americans has been attributed to the perfection of their machinery, which completely separates the external parts of the grain and makes the flour exceedingly fine and white.

USES.—It frequently lessens or removes toothache, especially that occurring in pregnancy or lactation (p. 353). It is useful in cases of chronic diarrhœa in children. It has been recommended in cases of rapid growth or deficient repair, as in growing children, anæmia, and debility from over-work, child-bearing, suckling, or diseases such as chronic abscess, diarrhœa, leucorrhœa, bronchitis, and phthisis. It is frequently given in rickets with considerable benefit, although it is well to combine it with cod-liver oil. It is often advantageously given, along with iron, in the form of Parrish's Chemical Food, containing two and a half grains of phosphate of calcium and one grain of phosphate of iron in every drachm.

Calcii Hypophosphis, B.P. and U.S.P. HYPOPHOSPHITE OF CALCIUM, $Ca(PH_2O_2)_2$, B.P. $CaH_4(PO_2)_2$; 170, U.S.P.

CHARACTERS.—Colourless or white six-sided prisms, or thin flexible scales, of a pearly lustre; permanent in dry air, odourless, having a nauseous, bitter taste and a neutral reaction.

REACTIONS.—The aqueous solution yields the reactions of calcium (p. 646).

DOSE.—1–10 grains.

OFFICINAL PREPARATION.

B.P.	U.S.P.	DOSE.
None	Syrupus Hypophosphitum......	1–2 fl. dr. (3·75 to 7·5 cc.).

U.S.P. Syrupus Hypophosphitum. SYRUP OF HYPOPHOSPHITES. Consists of the hypophosphites of calcium (35), of sodium (12), and of potassium (12); citric acid (1), spirit of lemon (2), sugar (500), water q.s. to make 1,000.

USES.—Hypophosphite of lime is useful in the early stages of phthisis (p. 717), and in nervous debility consequent upon overwork or worry. It may be given between two thin slices of bread and butter, if no irritability of the stomach be present. It is well to begin with a dose of two grains and gradually increase it, as otherwise it is apt to cause derangement of the digestion.

Calx Chlorinata, B.P.; Calx Chlorata, U.S.P. CHLORINATED LIME.—*Vide* CHLORINE (p. 549).

Calx Sulphurata, B. and U.S.P. SULPHURATED LIME.—A mixture (commonly misnamed sulphide of calcium) consisting chiefly of sulphide of calcium [CaS; 72] and sulphate of calcium [$CaSO_4$; 136], in varying proportions, but containing not less than 50 per cent. of absolute sulphide of calcium, B.P. (36 per cent. U.S.P.).

CHARACTERS.—A nearly white powder with a smell somewhat resembling that of sulphuretted hydrogen.

PREPARATION.—B.P. By calcining sulphate of calcium (7) with wood charcoal (1) when part of the sulphate is reduced to sulphide.

U.S.P. By calcining finely-powdered lime (100) with precipitated sulphur (90).

DOSE.—$\frac{1}{10}$–1 gr.

ACTION.—In large doses it is an irritant to the stomach, but medicinal doses usually cause no trouble, or at most slight discomfort, sometimes giving rise to eructations of sulphuretted hydrogen, and perhaps to some looseness of the bowels.

USES.—It is used chiefly for its effect on the process of suppuration, hastening the discharge of pus if already formed, and checking its formation if the inflammation be still in its early stage.

Sulphite of calcium in doses of $\frac{1}{10}$–1 gr. four or five times daily is said to do good in acne.

Class II.

Group I.—Appendix.

Aluminium. Cerium.

ALUMINIUM. Al; 27·5.

General Sources of Alum Salts.—Aluminium is very widely distributed in nature, clays being silicates of alumina. Two kinds of clay, **kaolin** and **fuller's earth**, being inert powders, are used as demulcents (pp. 347 and 446), and kaolin also as a pill-basis.

General Preparation.—It is prepared on a large scale from a kind of clay-slate called alum-schist. This contains a quantity of ferric sulphide. It is first roasted and moistened and exposed to air. The sulphur is thus converted into sulphuric acid, and ferrous sulphate and aluminium sulphate are formed. These are separated by lixiviation with water, and ammonium chloride is added. This forms ammonium sulphate, which combines with aluminium sulphate to form alum, ferrous chloride remaining in solution.

General Reactions of Alum Salts.—Salts of aluminium give a white gelatinous precipitate of hydrate with caustic potash or soda, soluble in excess; with ammonia a similar precipitate, insoluble in excess. The insolubility of the precipitate with ammonia in excess of the reagent readily distinguishes aluminium from zinc, which also gives a white precipitate with ammonium sulphide. Carbonates of potassium, sodium, and ammonium also precipitate the hydrate, which is insoluble in excess; ammonium sulphide also gives a white precipitate of hydrate.

General Impurities of Aluminium Salts.—The chief is sulphate of iron coming from the schist.

General Tests.—Alum should give no blue with either ferro- or ferricyanide of potassium.

Alumen, B. and U.S.P. Alum.—A sulphate of aluminium and potassium (potassium alum or potash alum), or of aluminium and ammonium (ammonium alum or ammonia alum), crystallised from solution in water, B.P.; a sulphate of aluminium and potassium, U.S.P. $K_2Al_2(SO_4)_4.24H_2O$; 948.

Characters.—B.P. In colourless transparent crystalline masses, exhibiting the faces of the regular octahedron, and having an acid sweetish astringent taste.

Reactions.—Its aqueous solution gives with caustic potash or soda a white precipitate soluble in an excess of the reagent (aluminium); and an immediate precipitate with chloride of barium (sulphate).

U.S.P. Large colourless octahedral crystals, acquiring a whitish coating on exposure to air; no smell, sweet astringent taste, and acid reaction.

Impurity.—Iron.

Test.—The solution in water does not acquire a blue colour from the addition of yellow or red prussiate of potash.

Dose.—10 to 20 grains.

PREPARATIONS.

B.P.	U.S.P.
Alumen exsiccatum.	Alumen exsiccatum.
Glycerinum Aluminis (1 in 5).	

Alumen Exsiccatum, B. and U.S.P. DRIED ALUM. $K_2SO_4Al_2(SO_4)_3$; 516.

PROPERTIES.—Dry white powder with the taste and other properties of alum.

PREPARATION.—By heating potassium alum until the water of crystallisation is driven off.

DOSE.—As an astringent, 10 to 40 grs.; as an emetic, 30 to 60 grs. For a lotion or gargle, 4 to 20 grs. to an ounce of water, or in the glycerinum aluminis, B.P.

ACTION.—Alum precipitates **albumen** and **gelatin.** It has no action on the unbroken **skin,** but when applied to parts from which the epidermis has been removed, it causes a film of coagulated albumen to form on the surface, and produces contraction of the tissues and vessels below. It thus lessens the supply of blood to the part, relieves congestion, diminishes the swelling, lessens the discharge from inflamed surfaces, and therefore acts as an **astringent.** By causing contraction of vessels and aiding the formation of coagula, it arrests hæmorrhage, and is therefore used either as a strong solution, or, if this prove insufficient, in the form of powder mixed with starch as a **styptic.** Dried alum abstracts water from the tissues and acts as a slight **caustic.** When swallowed in large quantities alum produces gastro-enteritis. In smaller doses it acts as an **emetic.** It is not so powerful as a caustic, astringent, styptic, or emetic as the salts of zinc or copper.

USES.—Dried alum is sometimes used to check exuberant granulation in ulcers. Bleeding from the nose may be stopped by sniffing up or injecting a solution of alum into the nostrils, and if the solution be ineffectual, powdered alum may be blown up by means of a paper funnel; it is also employed locally in bleeding from the mouth, throat, gums, hæmorrhoids, and the uterus. As an astringent, alum is used in both purulent and simple ophthalmia, but on account of its solvent action on the cornea it may lead to perforation, and should therefore be avoided (p. 216). A 1 per cent. solution, with 1 per cent. borax, is useful in acute eczema. It is used as a lotion in otorrhœa; as a wash to the mouth in ptyalism, aphthæ, and ulceration of the mouth and gums; as a gargle for sore-throat, congestion of the pharynx, and elongation of the uvula, as well as for the tickling, violent coughs which depend upon them, and are often accompanied by retching (p. 248). Dried alum has been applied in powder to remove the false membrane from the throat in croup and diphtheria.

Alum may be employed as a spray to the larynx in coughs and hoarseness depending upon chronic laryngeal catarrh. As a wash it may be used in inflammation of the vulva in children, to relieve itching in pruritis vulvæ, and to prevent the recurrence of prolapsus ani. It is useful as an injection in gonorrhœa and leucorrhœa.

When swallowed it will act on the stomach as an astringent, and is useful in **preventing** the **vomiting** of phthisis. It is not improbable that the vomiting which occurs usually after paroxysms of coughing is due to the congestion produced in the stomach by the cough, and that the alum prevents the vomiting by lessening this congestion (p. 377). When given in larger quantities alum is an **emetic**, acting promptly, and producing little depression. A teaspoonful of powdered alum proves a very useful emetic in cases of croup, and may be given to children mixed with honey. In the intestines alum acts as an **astringent** also, and is useful in diarrhœa; but, curiously enough, in lead colic it will act as a purgative, relieving the pain and opening the bowels. Its utility in lead-poisoning probably depends, to a considerable extent, on its being a sulphate, and thus precipitating any lead salts it may meet in the intestine in the form of insoluble lead sulphate, and preventing absorption from the intestinal canal. In typhoid fever, and in chronic dysentery and diarrhœa, it is said to be useful in checking the discharges from the bowels.

After its absorption into the blood it is supposed to exercise an astringent action, and is given to check sweating.

Internally, as a styptic, it is employed to check bleeding from the stomach, intestines, lungs, uterus, or kidneys.

ANTIDOTE.—Give tepid water with small doses of carbonate of sodium to decompose the alum, and empty the stomach by the stomach-pump or emetics.

U.S.P. Aluminii Hydras. HYDRATE OF ALUMINIUM. $Al_2(HO)_6$; 156.

CHARACTERS.—A white, light, amorphous powder, permanent in dry air, odourless, and tasteless.

SOLUBILITY.—It is insoluble in water or alcohol.

REACTIONS.—Soluble without residue in hydrochloric or in sulphuric acid, also in solution of potassa or of soda.

USES.—It is feebly astringent and desiccant. Is used externally as a powder in inflammatory diseases of the skin.

U.S.P. Aluminii Sulphas. SULPHATE OF ALUMINIUM. $Al_2(SO_4)_3.18H_2O$; 666.

CHARACTERS.—A white, crystalline powder, permanent in the air, odourless, has a sweet, and afterwards an astringent taste, and an acid reaction.

SOLUBILITY.—Soluble, without leaving more than a trifling residue, in 1·2 parts of water at 15° C. (59° F.), and very soluble in boiling water; almost insoluble in alcohol.

REACTIONS.—The aqueous solution of the salt yields the reactions of aluminium (p. 654) and of a sulphate (p. 595).

USES.—It is a powerful **antiseptic.** A saturated solution has been used as a mild caustic in enlarged tonsils, nasal polypi, nævi, scrofulous and cancerous ulcers, diseases of the os uteri, and various chronic enlargements. Weaker solutions are used as lotions to ulcers, and as injections in gonorrhœa, leucorrhœa, and fœtid discharges from the vagina.

A solution of the sulphate dissolves recently precipitated gelatinous alumina, and thus a benzoated solution of alumina can be prepared by saturating with gelatinous alumina 8 oz. of the sulphate in 1 pint of water, adding 6 drms. of powdered benzoin, keeping it at a temperature of 150° F. for six hours, and putting in a cool place for several days to allow the deposition of crystals. This solution is remarkable for its sweet odour and astringent balsamic taste.[1]

CERIUM. Ce; 92.

It is a rare metal.

Its salts are supposed to resemble those of bismuth and silver in their action.

Cerii Oxalas. OXALATE OF CERIUM, B. and U.S.P. $CeC_2O_4.3H_2O$, B.P.; $Ce(C_2O_4)_3.9H_2O$, U.S.P.

CHARACTERS.—It is a white granular powder, insoluble in water.

PREPARATION.—Is prepared by precipitating a soluble salt of cerium with oxalate of ammonium.

REACTIONS.—At a red heat it is decomposed into a reddish-brown powder, which dissolves completely in boiling hydrochloric acid without effervescence (oxide). The resulting solution gives a white crystalline precipitate of double sulphate of potassium and cerium when a saturated solution of sulphate of potassium is added to it.

IMPURITIES.—Aluminium, carbonates, and metals.

TEST.—When the salt is boiled with caustic potash and filtered, the filtrate is not affected by chloride of ammonium, showing that no aluminium is present: but when supersaturated with acetic acid it gives with calcium chloride a white precipitate of oxalate of calcium. The absence of carbonates and metals is ascertained by the usual tests.

DOSE.—1 to 10 grains. Large doses may succeed when small ones fail.

USES.—It was introduced by the late Sir James Simpson as a remedy to check the vomiting of pregnancy, and for this purpose is sometimes useful. It has also been employed in cases of chronic bronchitis and dyspnœa, and has been used also in nervous cough and nervous palpitation. It has been given, but with doubtful utility, in chorea and epilepsy.

[1] *United States Dispensatory*, 15th ed. p. 167.

Class II.

Group II.—Magnesium.

MAGNESIUM. Mg; 24.

Sources.—The chief source is dolomite, or mountain limestone, which consists of carbonates of magnesium and calcium. Magnesium is also found native as carbonate and silicate.

General Reactions of Magnesium Salts.—They give a gelatinous white precipitate with potash, soda, or ammonia, insoluble in excess, but soluble in a solution of ammonium chloride. They likewise give a white precipitate with potassium and sodium carbonates, but none with ammonium carbonate.

The characteristic test of magnesium is the formation of a precipitate of triple phosphate on the addition of ammonia and a soluble phosphate to a solution of a magnesium salt. Caustic ammonia itself throws down a precipitate of magnesium hydrate insoluble in excess, but soluble in ammonium chloride. As it is easier to prevent the precipitation of hydrate than to re-dissolve it when down, it is usual to add ammonium chloride first, then the ammonia, and lastly the phosphate of sodium.

General Preparation of Salts of Magnesium.

Is prepared	From	By
Magnesium sulphate, B. and U.S.P.	Dolomite . .	Dissolving in sulphuric acid; when soluble magnesium sulphate and insoluble calcium sulphate are formed.
Magnesium carbonate (heavy), B.P.	Magnesium sulphate	Precipitating with sodium carbonate, using hot concentrated solutions.
Ditto (light), B. and U.S.P.	Ditto . . .	Ditto, using dilute solutions in the cold.
Magnesia (heavy), B. and U.S.P.	Magnesium carbonate (heavy) . .	Calcining until all the carbonic acid is driven off, as shown by some taken from the centre of the crucible no longer effervescing on the addition of acid.
Ditto (light), B. and U.S.P.	Ditto (light). .	Calcining like the heavy magnesia.
Granulated citrate of magnesium, U.S.P.	Ditto . . .	Mixing with citric acid and water, drying and powdering. The powder is mixed with sugar, sodium bicarbonate, and citric acid, damped with alcohol, passed through a sieve, so as to form a coarse powder, and dried.
Magnesium sulphite, U.S.P.	Magnesia. . .	Suspending in water and adding excess of sulphurous acid.

General Impurities.—The chief impurities in the sulphate are the calcium and iron from dolomite. Other alkaline earths and alkalis may also be present. The sulphuric acid employed may be impure, or the sulphate may have been prepared by a process in which hydrochloric acid is used, and thus chlorides may occur. In the carbonate prepared from the sulphate the same impurities may occur, as well as unchanged sulphate. In magnesia these may all occur, and carbonate as well.

Tests.—The absence of iron and other metals is ascertained by the aqueous solution giving no colour or precipitate with ferrocyanide of potassium, hydrogen sulphide, or ammonium sulphide. Chloride of ammonium prevents the precipitation of magnesium by ammonia and ammonium carbonate, but it does not prevent the precipitation of other alkaline earths, and their absence is ascertained by the solution remaining clear after the addition of these three reagents.

General Action of Magnesium.—When administered by the mouth the difference between absorption and excretion (p. 39) is not great enough to allow magnesium salts to accumulate in the blood sufficiently to produce any toxic effects. When injected into the blood, sulphate of magnesium, in doses of about 5 grs. per pound of body weight, abolishes reflex action, and paralyses the respiration and heart in cats (Hay), and has a similar effect in other animals also.

Magnesii Sulphas, B. and U.S.P. Sulphate of Magnesium. Epsom Salts. $MgSO_4.7H_2O$; 246.

Properties.—In minute, colourless, transparent, acicular crystals, whose form is a rhombic prism. They look exactly like sulphate of zinc. Its taste is bitter, and it is called in Germany *Bittersalz*. This distinguishes it from zinc sulphate, which has a strong metallic taste.

Solubility.—It readily dissolves in water.

Reactions.—The solution gives the reactions of magnesium (p. 658) and a sulphate (p. 595).

Impurities.—Calcium and iron.

Tests.—Its aqueous solution is not precipitated at ordinary temperatures by oxalate of ammonium (no calcium), nor does it give a brown precipitate with chlorinated lime or soda (no iron).

Dose.—As a purgative, half an ounce to an ounce and a half for a single dose. In repeated doses, especially if taken fasting, 60 to 120 grains. As a diuretic, 20 to 60 grs.

Officinal Preparations.

B.P.	U.S.P.
Enema Magnesii Sulphatis.	Infusum Sennæ Compositum.
Mistura Sennæ Composita.	

B.P. Enema Magnesii Sulphatis. Enema of Sulphate of Magnesium (Enema Catharticum).—Sulphate of magnesium 1, olive oil 1, starch mucilage 15.

Action.—Sulphate of magnesium to saturation precipitates globulins.

In moderate doses it causes a copious secretion from the intestinal mucous membrane, and acts as a **purgative**. It does not stimulate the muscular coat of the bowels much; it thus

causes little griping. As it does not accelerate peristaltic action, a part of the fluid poured out into the intestine may be reabsorbed as it passes slowly along. It is therefore usual when we wish to produce free purgation to combine the salt with some purgative which will stimulate the muscular coat of the bowel, such as senna or cascara sagrada. When given alone it is apt to produce much flatulent distension of the abdomen and rumbling, and a carminative is therefore often given along with it. Its objectionable bitter taste may be covered by dissolving it in acid infusion of roses and adding spirit of chloroform. It may be employed as a purgative enema. When absorbed into the blood it acts as a **diuretic** if the skin be kept cool, and as a **diaphoretic** if the skin be kept warm or moderate exercise be taken. It is absorbed more readily when given in small quantities, but a little is also taken up when purgative doses are employed, and it is therefore a useful purgative in febrile states.

USES.—Sulphate of magnesium is one of the most common and useful saline purgatives. For its mode of action and uses, *vide* pp. 391–394. On account of its great solubility it may be used in very concentrated solution to remove dropsy (p. 394) when less soluble salts cannot. Repeated small doses are very serviceable in biliousness.

U.S.P. Magnesii Carbonas. CARBONATE OF MAGNESIUM. $(MgCO_3)_4Mg(HO)_2.4H_2O$; 484. This corresponds to the two kinds mentioned in the B.P.

B.P. Magnesii Carbonas. CARBONATE OF MAGNESIUM. $(MgCO_3)_3Mg(HO)_2.4H_2O$.

B.P. Magnesii Carbonas Levis. LIGHT CARBONATE OF MAGNESIUM. $(MgCO_3)_3Mg(HO)_2.4H_2O$.

Both the light and heavy carbonates of magnesium have the same chemical composition, and differ only in their weight.

PROPERTIES.—A white granular powder almost tasteless.

PREPARATION.—Both are prepared by precipitating a solution of sulphate of magnesium by a solution of carbonate of sodium; removing the resulting sulphate of sodium, washing the carbonate, and drying it at a temperature not exceeding that of boiling water so as not to decompose it.

In preparing the heavy carbonate, concentrated boiling solutions are used, the mixture evaporated to dryness, and the sulphate of sodium removed by subsequent digestion with water. In preparing the light carbonate, dilute solutions are employed: they are mixed cold; boiled for fifteen minutes; and the sulphate of sodium separated by filtration.

REACTIONS.—It is recognised as a carbonate by dissolving with effervescence in hydrochloric acid, and the magnesium is detected by the appropriate tests in the resulting solution (p. 658). The two carbonates are distinguished by their weight.

ACTION.—When swallowed, carbonate of magnesium will have a less stimulating effect upon the mucous membrane than potash or soda, as it is nearly insoluble; but on this very account it is

to be preferred to them for neutralising acid in the stomach after meals, inasmuch as it will only neutralise the excess of acid without rendering the fluids alkaline. In the intestine it acts as a laxative, and is partly excreted in the fæces and partly converted into magnesium salts which are absorbed and pass out in the urine.

USES.—As an **antacid** and **laxative**, especially in children; in heartburn, in dyspepsia, and vomiting during pregnancy; and in cases where it is desirable to render the urine alkaline, as in gouty persons, where potash and soda disagree.

DOSE.—As an antacid, 5 to 20 grains; as a laxative, 10 to 60 grains. It may be conveniently given in milk.

OFFICINAL PREPARATIONS.

B.P. DOSE.

Liquor Magnesii Carbonatis, as antacid, 1–4 fl. dr.; as laxative, 1–2 fl. oz.
„ „ **Citratis,** as laxative,.....5–10 fl. oz.

U.S.P.

Mistura Magnesii et Asafœtidæ.................. $\frac{1}{2}$ fl. oz.

B.P. Liquor Magnesii Carbonatis. SOLUTION OF CARBONATE OF MAGNESIUM.—It is a solution of carbonate of magnesium in water containing carbonic acid. It contains about $13\frac{1}{2}$ grains in the fluid ounce. It is a pleasant laxative for children; and laxative and antacid for women, especially useful during pregnancy.

B.P. and U.S.P. Liquor Magnesii Citratis. SOLUTION OF CITRATE OF MAGNESIUM.—Dissolve citric acid, 200 grains, in 2 ounces of water, add carbonate of magnesium 100 grains, and stir until it is dissolved. Filter the solution into a strong half-pint bottle, add syrup of lemons $\frac{1}{2}$ fl. oz. and enough water nearly to fill the bottle; then introduce bicarbonate of potassium in crystals 40 grains, and immediately close the bottle with a cork, which should be secured with string or wire. Afterwards shake the bottle until the bicarbonate of potassium has dissolved.

U.S.P. Mistura Magnesii et Asafœtidæ (Dewees' Carminative).—Carbonate of magnesium 5, tincture of asafœtida 7, tincture of opium 1, sugar 10, distilled water up to 100. DOSE.—$\frac{1}{2}$ fl. oz. in hysterical flatulence.

Magnesia Levis, B.P.; Magnesia, U.S.P. MAGNESIA. LIGHT MAGNESIA, MgO; 40.

PREPARATION.

U.S.P.

Trochisci Magnesiæ (3 grs. in each).

Magnesia Ponderosa, B. and U.S.P. HEAVY MAGNESIA.

CHARACTERS.—Both are white powders differing from each other only in their weight, which is $3\frac{1}{2}$ to 1.

SOLUBILITY.—They are insoluble in water, but dissolve in acids without effervescence.

REACTIONS.—The solution in acids exhibits the reactions of magnesium.

DOSE.—10 to 60 grains of either heavy or light.

ACTION AND USES.—Like those of the carbonate.

OFFICINAL PREPARATION.

Pulvis Rhei Compositus, 2 parts of heavy magnesia in 3.

CHAPTER XXVI.

METALS—(*continued*).

Class II.—DYAD METALS—(*continued*).

General Actions of Heavy Metals.—The heavy metals form compounds with albumen, known as **albuminates.** These are sparingly soluble, and in consequence of this, white of egg is a useful antidote in poisoning with heavy metals. Albuminates of copper have been obtained by Harnack in which the proportion of copper is definite, and is either 1·35 or 2·64 per cent. On account of their affinity for albumen the heavy metals combine with the albuminous constituents of the **tissues,** and act as powerful **astringents** (p. 349), **irritants** (pp. 341 and 395), or **caustics** (pp. 344 and 346), according to the strength of the application. Their action is comparatively slight when they are applied to the unbroken skin, as the epidermis forms an obstacle to their action, but it is strongly marked where the epidermis is absent, as in wounds or ulcers, and on mucous surfaces where the epithelium is soft. In addition to their astringent action on the fluids and tissues, two metals—lead and silver—cause contraction of the **blood-vessels** (p. 349). In considering the action of the heavy metals belonging to this group and those belonging to Classes III.–VIII., on the organism, it is necessary to distinguish carefully between—

(1) The **local action** upon the surface of the body or upon the alimentary canal, with the **reflex effects** upon the nervous, respiratory and circulatory systems consequent on this local action, and—

(2) The effects produced on the various organs of the body by the metal **after its absorption.** Thus, a large dose of corrosive sublimate when swallowed may produce the ordinary symptoms of irritant poisoning, causing vomiting and purging by its local action on the stomach and intestine, and producing reflexly general collapse with feeble circulation and respiration. Yet if the treatment be prompt, none of the metal may be absorbed, and thus the symptoms which would be produced by its action on the various organs when carried to them by the circulation may be absent.

In considering the effects produced by a metal after its absorption, we must remember that the nature of its **action differs**

according to the quantity present in the blood at any one time, and that this quantity depends on the relation between the rapidity of absorption and excretion (p. 39).

The proportion between absorption and excretion depends greatly on the channel of introduction, and therefore the same drug may produce quite different effects according to the mode of its administration. Thus solution of perchloride of iron, when injected directly into the veins, will cause almost immediate death from coagulation of the blood. Other salts of iron which have no coagulating action, if injected into the circulation, produce paralysis of the central nervous system and of the vaso-motor nerves, causing loss of voluntary motion, an enormous fall of the blood-pressure, and death. When injected subcutaneously iron is absorbed, but it enters the blood less rapidly than when injected into the veins, the quantity present in the blood at any one time is less, and these symptoms are not produced. Nevertheless absorption takes place from the subcutaneous tissue so rapidly that enough iron enters the blood to produce a toxic action. But this action, instead of affecting the nerves, is chiefly exerted on the excreting system, and inflammation of the kidneys occurs. When taken into the intestinal canal iron is absorbed very slowly, and only a very small quantity appears in the urine. It is hard to say whether the slight headache which is apt to come on from the administration of iron is due to the direct action of the metal on the nerve-centres after its absorption, or is merely reflex and due to the action of the metal on the intestine. No injury is done to the kidneys of healthy persons, though the effect of the iron upon these organs may be manifested by the diminution of albumen in cases of renal disease.

The form in which metals are absorbed from the intestinal canal is probably that of albuminates, or, perhaps, more properly, of peptonates.

The only heavy metals which are rapidly absorbed from the healthy intestinal canal are lead, mercury, and arsenic. Copper, zinc, silver, tin, iron, manganese, nickel, and cobalt are absorbed very slowly indeed. This is shown by the fact that when given internally only mere traces of them appear in the urine. That their absence from this secretion is due to non-absorption, and not to their retention in the blood or tissues, is proved by the fact that when they are injected subcutaneously they pass readily through the kidneys.

Contrary to one's expectation, it has been found that metals are much more readily absorbed by the gastro-intestinal mucous membrane when it is in a catarrhal condition than when it is in a healthy state. When large doses of metallic salts are given at once they are very apt to produce acute catarrh of the intestinal canal, and they are then readily absorbed, and appear in large quantity in the urine. If small doses are given at first, instead

of large ones, they may be gradually increased without producing any catarrh, and then absorption into the blood and excretion by the urine does not occur, or only to a slight extent, although the dose finally reached may be large.

The therapeutic bearing of this fact is that if we wish to affect the kidneys by metallic remedies, e.g. by iron in cases of albuminuria, the best method of administering the remedy is to begin with large doses at once.

After absorption into the **blood** the metals probably remain, to a great extent, if not entirely, in the plasma, and do not become combined with the corpuscles, or only to a very slight extent.[1]

They are carried to all parts of the body, and probably unite with certain **tissues.** They remain in combination with the tissues for a greater or less length of time, modifying their nutrition and functional activity, and then, being again set free, they become excreted.

The heavy metals have all a powerful poisonous action on **muscles, nerves, nerve-centres, and glands.** The slightness of the action which they exert on these structures when administered by the alimentary canal is due to their slow and sparing absorption by it. But their poisonous power at once becomes evident, as in the case of iron, when they are injected either subcutaneously or directly into the circulation in the form of double salts or organic compounds, which produce no local irritation at the point of injection, nor coagulation of the blood when they are introduced directly into the vessels. The alterations in the spinal cord in acute poisoning by some of them—e.g. lead and mercury, and also by arsenic—have the characters of acute central myelitis, the grey substance being chiefly affected. In more chronic poisoning the white substance is affected as well, so that the alterations resemble those of diffuse myelitis. The nervous symptoms produced by heavy metals are probably due to such alterations in the nerve-centres, and sometimes to peripheral alterations in the nerves also.

Metals are **excreted** chiefly by the bile (p. 405), by the kidneys, by the mucous membranes of the stomach and intestine; and probably to a slight extent by the skin. Elimination by these channels may commence very soon after the metal has entered the blood.

During the process of elimination the metals may irritate the eliminating organs (Fig. 5, p. 39), and may cause vomiting by their action on the stomach (p. 372), diarrhœa by their action on the intestine, and albuminuria by their action on the kidneys, although

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[1] This is best shown by separating the corpuscles and plasma in a centrifugal machine and analysing them separately, so as to ascertain the amount of metal in each.

they have been injected into the veins, or subcutaneously, and only reach these organs through the blood.

On account of the quantity of metal which is eliminated by the bile and intestinal mucous membrane, purgatives are useful agents in the treatment of chronic metallic poisoning (cf. pp. 384 and 561).

When metals have entered the blood in considerable quantities, the **kidneys** become inflamed during the process of their excretion, and undergo changes which affect both the tubules and the glomeruli. The tubules are affected first, and the epithelial cells, both of the convoluted and straight tubules, take up the metal and become gradually disintegrated. They are partly thrown out as casts, and partly block up the tubules, causing secondary degeneration of the glomeruli. Both tubules and glomeruli become atrophied. These effects appear to be produced by all the heavy metals.

The possible effect of mercury on the kidneys should be borne in mind when prescribing a very prolonged mercurial course, and it would be interesting to inquire how far albuminuria in apparently healthy persons is caused by mercurials (cf. p. 20).

GROUP III.—ZINC, COPPER, *Cadmium*, AND SILVER.

GENERAL ACTIONS.—They combine with **albumen** and form insoluble albuminates, and have thus an astringent action.

With the exception of salts of silver, which form a compound with the epidermis, they have no action on the epidermis, but they may pass through the pores, especially chloride of zinc. This salt produces inflammation, or even mortification, acting by its affinity both for water and for albumen. It is used as a caustic for destroying the surface of unhealthy sores and producing a more healthy action. The other preparations of the metals in this group act in the same way, but are less powerful, and are applied to ulcers and to chronic skin-diseases.

They are applied for their astringent action to the **eye** in gonorrhœal ophthalmia, ulcerations or opacity of the cornea, and to the **mucous membranes** of the urethra and vagina in gonorrhœa and leucorrhœa.

Insoluble preparations such as oxide of zinc have little action on the skin, but are applied as powder or ointment to raw and excoriated surfaces, where protection from external influences with very slight stimulation is wished, as in intertrigo.

In the **mouth** they combine with the albumen of the tongue and cheeks, and produce a very disagreeable metallic taste. Notwithstanding this they are employed, especially sulphate of copper, for ulcers of the mouth or fauces.

Zinc chloride has been recommended for carious teeth.

In the **stomach** they unite with the albumen in its walls, producing irritation and consequent nausea, accompanied by muscular relaxation. They have been used as nauseants in spasmodic affections, as epilepsy, chorea, hysteria, &c.

In a somewhat larger dose they produce vomiting, which is speedy and complete, especially in the case of zinc and copper, which are consequently much used in cases of poisoning where we wish the stomach emptied with all possible speed. They are preferred in such cases to tartar emetic, as they do not produce so much depression, nor are they so liable to cause diarrhœa; and to ipecacuanha, because their action is more rapid and certain.

The compounds of zinc or copper with albumen or peptones will produce vomiting, either when given by the mouth or when injected into the veins, but they are classed as **local emetics** (p. 373).

Their emetic action when injected into the veins may be due to a direct action on the vomiting centre in the medulla (p. 371); but it may also be that they are carried to the stomach by the blood and act reflexly from it (*vide* Fig. 5, p. 39, and cf. p. 373).

The albuminates of copper and zinc, and probably those of the other metals, undergo changes both in the stomach and intestine before absorption which we do not perfectly understand. Albumen is not simply dissolved and absorbed in the intestinal canal, but is converted into peptone. Albuminate of copper has been introduced into a gastric fistula in a dog, and the blue colour was seen to disappear at the edges, and finally all copper was removed from it before the albumen was itself completely digested. Whether or not the copper was removed in combination as a peptone or not we cannot as yet say. Copper salts unite with peptone, forming an easily soluble compound.

In the **intestine** small doses lessen the frequency of the stools, and have been thus used in chronic diarrhœa and dysentery, but larger doses have an irritant effect and cause diarrhœa. The insoluble salts, as oxide and carbonate of zinc, have a much weaker action than the soluble ones, and thus a large quantity of them has the same action as a small one of the soluble salts.

Chronic poisoning by copper is said to have occurred in consequence of the use of copper salts to give a bright green colour to tinned peas or other vegetables, as well as from the employment of imperfectly cleansed copper pans. Some doubt has been thrown on the possibility of producing chronic poisoning by the internal administration of copper in small doses, as in some experiments it was given to animals for a length of time without injury. More recent experiments show, however, that at least in ruminants chronic poisoning may be produced. The symptoms are loss of appetite, imperfect rumination, periodical constipation, imperfect nutrition, muscular weakness, languor,

jaundice, albuminuria, and towards the end hæmoglobinuria or hæmaturia. On *post-mortem* examination granular degeneration of the muscles and heart, enlarged spleen, fatty degeneration of the liver, dark brown colour of the blood, and granular deposits of methæmoglobin in the renal tubules, along with hæmorrhagic parenchymatous nephritis, are found.

Chronic poisoning by copper may occur among coppersmiths, or in families where copper pans have been used. The symptoms are a metallic taste, a feverish state, with symptoms of subacute gastro-enteritis, not unfrequently jaundice, trembling of limbs, and cramps. A purple line is said to form on the gums.

ZINC. Zn; 64·9.

Sources of Zinc.—The chief are native carbonate or calamine ($ZnCO_3$) and zinc blende (ZnS).

General Reactions of Zinc Salts.—The most characteristic test is that it forms a white sulphide, which is precipitated on the addition of ammonium sulphide to a solution, and which is insoluble in caustic alkalies. Caustic potash, soda, or ammonia give a white precipitate of hydrate, soluble in excess; ammonium carbonate gives a similar precipitate, soluble in excess; but sodium and potassium carbonate give a white precipitate, insoluble in excess.

General Preparation of Zinc Salts.

<table>
<tr><th>Prepared</th><th>From</th><th>By</th></tr>
<tr><td>Zinc, B. and U.S.P. .</td><td>Zinc blende or calamine</td><td>Roasting, to drive off sulphur or carbonic acid, and then distilling the oxide with charcoal.</td></tr>
<tr><td>Granulated zinc, B.P.</td><td>Zinc . . . .</td><td>Melting and throwing into water.</td></tr>
<tr><td>Zinc chloride, B. and U.S.P.</td><td>Zinc . . . .</td><td>Dissolving in hydrochloric acid ($Zn_2 + 4HCl = 2ZnCl_2 + 2H_2$): it is then purified from lead or iron by passing chlorine through it, and adding carbonate of zinc,
$\underset{\text{Ferrous chloride}}{2FeCl_2} + \underset{\text{Chlorine}}{Cl_2} = \underset{\text{Ferric chloride.}}{Fe_2Cl_6}$.
$\underset{\text{Ferric chloride}}{Fe_2Cl_6} + \underset{\text{Carbonate of zinc}}{3ZnCO_3} + 3H_2O =$
$\underset{\text{Ferric hydrate}}{Fe_2(HO)_6} + \underset{\text{Chloride of zinc}}{3ZnCl_2} + \underset{\text{Carbonic acid gas.}}{3CO_2}$.
$\underset{\text{Chloride of lead}}{PbCl_2} + \underset{\text{Chlorine}}{Cl_2} + \underset{\text{Carbonate of zinc.}}{2ZnCO_3} =$
$\underset{\text{Peroxide of lead}}{PbO_2} + \underset{\text{Chloride of zinc}}{2ZnCl_2} + \underset{\text{Carbonic acid gas.}}{2CO_2}$.</td></tr>
<tr><td>Zinc sulphate, B. and U.S.P.</td><td>Zinc . . . .</td><td>Dissolving in sulphuric acid, and purifying in the same way as chloride.</td></tr>
<tr><td>Zinc carbonate, B. and U.S.P.</td><td>Zinc sulphate .</td><td>Precipitating with carbonate of sodium.</td></tr>
</table>

GENERAL PREPARATION OF ZINC SALTS—*continued.*

Prepared	From	By
Zinc acetate, B. and U.S.P.	Zinc carbonate . .	Dissolving in acetic acid.
Zinc oxide, B. and U.S.P.	Ditto . .	Calcining.
Zinc oleate, B.P. .	Zinc oxide . .	By dissolving in oleic acid.
Zinc valerianate, B. and U.S.P.	Zinc sulphate . .	Mixing with sodium valerianate.
Zinc bromide, U.S.P.	Ditto . .	Mixing with hot solution of potassium bromide, precipitating potassium sulphate by alcohol, filtering and evaporating. Or by acting on zinc with bromine.
Zinc iodide, U.S.P. .	Zinc	Digesting with iodine in water and evaporating.
Zinc phosphide. U.S.P.	—	Passing phosphorus vapour in dry hydrogen over melted zinc.
Zinc sulphocarbolate, B.P.	Zinc oxide . .	Heating a mixture of carbolic acid and sulphuric acid, saturating the product with zinc oxide, evaporating and crystallising.

GENERAL IMPURITIES OF ZINC SALTS.—Iron, lead, copper, and arsenic.

GENERAL TESTS.—A solution of zinc salt acidulated with hydrochloric acid gives no precipitate with sulphuretted hydrogen (absence of lead, copper, or arsenic). The absence of copper is further ascertained by ammonia giving with a solution of zinc salts a white precipitate, soluble in excess without colour. If copper be present the solution would be blue. Solutions should give no blue with ferro- or ferri-cyanide of potassium, nor any black colour with tincture of galls (absence of iron).

GENERAL ACTION OF SALTS OF ZINC.—They combine with albumen and coagulate it. The chloride of zinc thus acts as an **escharotic** after the epidermis has been previously removed by caustic potash. Neither it, nor the sulphate, nor acetate of zinc has any action on the unbroken skin, but when applied to mucous membranes, they will act as **irritants** in large, and as **astringents** in small doses.

Sulphate and acetate of zinc are prompt **emetics**, causing rapid evacuation of the contents of the stomach with little nausea or depression.

The mode of action of zinc salts as emetics has not been perfectly determined. It is probably partly due to the **local** effect upon the stomach, and partly to the stimulant action upon the vomiting centre in the medulla oblongata after absorption into the circulation.

Vomiting is produced by the injection of zinc salts into the circulation, but this may be partly due to irritation of the stomach by the zinc salts during the process of excretion by its mucous membrane, as well as to the action upon the medulla.

In small doses zinc salts act also as **nervine tonics**, and lessen sweating.

Zincum. B. and U.S.P. ZINC. 64·9. Zinc of commerce, B.P. Metallic zinc in the form of thin sheets or irregular granulated pieces, U.S.P.

CHARACTERS.—A bluish-white metal having the sp. gr. 6·9.

REACTIONS.—When treated with warm diluted sulphuric acid it is almost completely dissolved, forming a colourless liquid which yields a white precipitate with test solution of ferro-cyanide of potassium, or of sulphide of ammonium. U.S.P.

PREPARATIONS CONTAINING ZINC.

B.P.	U.S.P.
Liquor Zinci Chloridi.	Liquor Zinci Chloridi.
Oleatum Zinci.	Unguentum Zinci Oxidi.
Unguentum Zinci.	Zinci Acetas.
„ „ Oleati.	„ Bromidum.
Zinci Acetas.	„ Carbonas Præcipitatus.
„ Carbonas.	„ Chloridum.
„ Chloridum.	„ Iodidum.
„ Oxidum.	„ Oxidum.
„ Sulphas.	„ Phosphidum.
„ Sulphocarbolas.	„ Sulphas.
„ Valerianas.	„ Valerianas.
Zincum Granulatum.	

B.P. Zincum Granulatum. GRANULATED ZINC—(Zinc fused and poured into water).

IMPURITIES.—Very frequently it contains sulphur or arsenic.

TESTS.—Zinc is chiefly used for preparing hydrogen, and these impurities are tested by adding pure dilute hydrochloric or sulphuric acid to it and holding over it a piece of paper dipped in acetate of lead. If sulphur be present the paper is blackened. If the piece of paper be wetted with solution of nitrate of silver, a brown or black stain is produced if arsenic is present. On lighting the hydrogen and depressing a piece of porcelain on it, a black stain is produced if arsenic is present.

Zinci Oxidum, B. and U.S.P. OXIDE OF ZINC. ZnO. 80·9.

CHARACTERS.—A soft, nearly white, tasteless and inodorous powder, becoming pale-yellow when heated.

IMPURITIES.—Undecomposed carbonate, chloride, sulphates, iron and copper.

TESTS.—Dissolves without effervescence in diluted nitric acid, forming a solution, which is not affected by chloride of barium or nitrate of silver, and gives with carbonate of ammonium a white precipitate which dissolves entirely (no iron) without colour (no copper) in an excess of the reagent, forming a solution which is precipitated white by sulphide of ammonium.

DOSE.—2 to 10 grains.

OFFICINAL PREPARATIONS.

B.P.	U.S.P.
Unguentum Zinci.	Unguentum Oxidi Zinci.

B.P. Unguentum Zinci. ZINC OINTMENT.—Oxide of zinc 80 grs., benzoated lard 1 oz., or 1 in 6½ nearly.

U.S.P. Unguentum Oxidi Zinci. OINTMENT OF OXIDE OF ZINC.—Oxide of zinc 20, benzoated lard 80, or 1 in 5.

USES.—Oxide of zinc is sparingly soluble in the stomach. It dissolves to a slight extent, too little to act as an emetic, but sufficient to produce the action of small doses of soluble zinc salts as a nervine tonic and astringent.

It may be used as a dusting powder in intertrigo, and the zinc ointment is one of the most efficacious remedies we possess for application to excoriated surfaces. In acute eczema, zinc ointment can sometimes be borne, when other forms of bland ointment only increase the inflammation, and in acute vesicular eczema, dabbing the part for about fifteen minutes with black wash and then rubbing in zinc ointment gently is sometimes a very successful treatment. It has been given in whooping-cough, epilepsy, hysteria, nervous headache, and to check profuse sweating in phthisis, and profuse secretion from the bronchi in bronchitis. In the sweating of phthisis it is frequently combined with hyoscyamus, and it is somewhat difficult to say how much of the beneficial action is due to the hyoscyamus.

B.P. Oleatum Zinci. OLEATE OF ZINC (p. 591).

B.P. OFFICINAL PREPARATION.

Unguentum Zinci Oleati (oleate of zinc 2, benzoated lard 11).

USES.—Ointment of oleate of zinc alone, or along with oleate of morphine, is an excellent preparation in many cases of acute eczema and of intertrigo.

B.P. Calamina Præparata. PREPARED CALAMINE.—Native carbonate of zinc calcined in a covered earthen crucible at a moderate temperature, powdered and freed from gritty particles by elutriation.

CHARACTERS.—A pale pinkish-brown powder, without grittiness.

SOLUBILITY.—It is almost entirely soluble, with effervescence, in acids.

OFFICINAL PREPARATION.

Unguentum Calaminæ (prepared calamine 1, benzoated lard 5).

USES.—Used sometimes instead of oxide. In skin diseases preferred to the oxide by some, especially in weeping eczema; it is still better applied in the form of a lotion, e.g. calamine 40 grs., oxide of zinc 20 grs., glycerine 20 min., water to 1 oz., or prepared calamine 12 grs., prepared chalk 24 grs., lime water 1 oz.

Zinci Carbonas, B.P.; Zinci Carbonas Præcipitatus, U.S.P. CARBONATE OF ZINC. B.P. PRECIPITATED CARBONATE OF ZINC. $ZnCO_3(ZnO)_2.3H_2O$. B.P.; $(ZnCO_3)_2.3Zn(HO)_2$; 546·5, U.S.P.

CHARACTERS.—White, tasteless, inodorous.

SOLUBILITY.—It is insoluble in water; soluble, with effervescence and without residue, in dilute nitric acid.

REACTIONS.—The solution in nitric acid gives the reactions of zinc (p. 667).

DOSE.—1 to 10 grains.

USES.—Like those of calamine.

Zinci Chloridum, B. and U.S.P. CHLORIDE OF ZINC, $ZnCl_2$; 135·7.

CHARACTERS.—Colourless opaque rods or tablets, very deliquescent and caustic.

SOLUBILITY.—It is soluble almost entirely in water, alcohol, and ether.

REACTIONS.—The watery solution gives the reactions of zinc and of a chloride (p. 594).

PREPARATION CONTAINING CHLORIDE OF ZINC.

Liquor Zinci Chloridi ....366 grains in one fluid ounce.

Liquor Zinci Chloridi, B. and U.S.P. SOLUTION OF CHLORIDE OF ZINC, $ZnCl_2$; 135·7, U.S.P. Prepared like the solid, but not so much evaporated.

USES.—It is a powerful **caustic** distinguished by its property of burning **deeply** and not spreading sidewise like many others. It is applied, in substance, or made into a paste with starch or gypsum, to cancers, sloughing or unhealthy sores, and nævi. Diluted it is applied to ulcers.

It has been used to destroy the exposed pulp in decayed teeth, warty growths, condylomata, syphilitic sores, and lupus. In the proportion of one to two grains in a pint of water it has been recommended by Ringer as an injection in gonorrhœa.

Burnett's (Sir W.) disinfectant and deodorising solution is solution of chloride of zinc (of sp. gr. 2), and it is by the accidental use of this, that most cases of zinc-poisoning occur.

Zinci Sulphas, B. and U.S.P. SULPHATE OF ZINC. $ZnSO_4.7H_2O$; 286·9.

CHARACTERS.—In colourless transparent prismatic crystals with a strong metallic styptic taste.

REACTIONS.—Its solution in water gives the reactions of zinc and of a sulphate (p. 595).

DOSE.—1 to 3 grains as a tonic; 10 to 30 grains as an emetic.

USES.—Sulphate of zinc is used as an **astringent** to lessen discharges from mucous membranes; it is employed as a lotion in gonorrhœa and leucorrhœa; as a wash to the eye in ophthalmia; and, mixed with honey, in gangrene of the mouth in children. It is used as a gargle to the throat in relaxed sore-throat, pendent uvula, and enlarged tonsils.

As an **emetic** it is chiefly employed in narcotic poisoning, where the rapidity of its action, unaccompanied by any depressing influence on the circulation, is very serviceable. It is sometimes used, also, to cause vomiting in croup. It is employed as an **astringent** in chronic diarrhœa and dysentery. It has also been used as a **tonic** in flatulence and flatulent distension of the colon. After absorption into the blood it has a tonic action on some parts of the nervous system, and is used in the treatment of convulsive diseases, such as chorea, epilepsy, hysteria, as well

as in spasmodic affections of involuntary muscular fibre, such as angina pectoris and spasmodic asthma.

Zinci Sulphocarbolas, B.P. SULPHOCARBOLATE OF ZINC. $Zn(C_6H_5SO_4)_2.H_2O$.

CHARACTERS.—Colourless, transparent, tabular, efflorescent crystals, with an astringent taste.

SOLUBILITY.—Soluble in about twice the weight of rectified spirit and of water.

REACTIONS.—The watery solution is coloured violet by perchloride of iron, and gives a white precipitate with sulphydrate of ammonium; it is made faintly turbid by chloride of barium, and it is not precipitated by oxalate of ammonium.

ACTION.—Sulphocarbolate of zinc is **antiseptic** and **astringent.**

USES.—It is used as an injection in otorrhœa, gonorrhœa, and other cases of purulent discharges, in the strength of 2 to 4 grains to the ounce of water. It is not given internally.

Zinci Acetas, B. and U.S.P. ACETATE OF ZINC. $Zn(C_2H_2)_2(CO.OH)_2.2H_2O$; 218·9, B.P.; $Zn(C_2H_3O_2)_2.3H_2O$; 236·9, U.S.P.

CHARACTERS.—Thin, translucent and colourless crystalline plates, of a pearly lustre, with a sharp unpleasant taste.

SOLUBILITY.—Soluble in water.

REACTIONS.—The solution gives the reactions of zinc, and evolves acetic acid when decomposed by sulphuric acid.

DOSE.—1 to 2 grains as a tonic; 10 to 20 grains as an emetic.

USES.—It is used for much the same purposes, and in the same doses, as the sulphate. An unchemical but useful injection for gonorrhœa, gleet, and leucorrhœa, consists of six grains of sulphate of zinc, with four ounces of the dilute solution of subacetate of lead. In this mixture the sulphate of lead which is precipitated has probably a beneficial action in keeping apart the surfaces of the mucous canal into which it is injected (p. 446).

U.S.P. Zinci Bromidum. BROMIDE OF ZINC. $ZnBr_2$; 224·5.

CHARACTERS.—A white, or nearly white, granular powder, very deliquescent, odourless, having a sharp saline metallic taste, and a neutral reaction.

SOLUBILITY.—Very soluble in water and in alcohol.

REACTIONS.—The aqueous solution of the salt yields the reactions of zinc and of a bromide (p. 594).

DOSE.—2 to 8 grains given in syrup.

USES.—In large doses it is irritant and emetic like other salts of zinc. It has been recommended in epilepsy with the idea of combining the actions of bromine and zinc.

U.S.P. Zinci Iodidum. IODIDE OF ZINC. ZnI_2; 318·1.

CHARACTERS.—A white, or nearly white, granular powder, very deliquescent, odourless, having a sharp saline and metallic taste, and an acid reaction.

SOLUBILITY.—Very soluble in water and in alcohol.

REACTIONS.—The aqueous solution yields a white precipitate with test solution of ferrocyanide of potassium or of sulphide of ammonium, a yellow precipitate with test solution of acetate of lead, and a red one with test solution of mercuric chloride (iodide).

DOSE.—½ to 2 grains.

USES.—Locally it has been used in solution as an application to enlarged tonsils. An ointment, 1 part to 8 of lard, has been used in place of the ointment of iodide of potassium or of cadmium to reduce swellings. A solution of 2 grains to 1 oz. has been used in gonorrhœa. Internally it has been used in scrofula, chorea, and hysteria. It is best administered in the form of syrup.

Zinci Valerianas, B. and U.S.P. VALERIANATE OF ZINC. $Zn(C_5H_9O_2)_2.H_2O$; 284·9.

CHARACTERS.—In brilliant, white, pearly, tabular crystals, with a feeble odour of valerianic acid, and a metallic taste.

SOLUBILITY.—It is scarcely soluble in cold water or in ether, but is soluble in hot water and alcohol.

REACTIONS.—Heated to redness in an open crucible, it leaves a residue which, when dissolved in diluted sulphuric acid, yields with ammonia a precipitate which entirely dissolves in an excess of the reagent, and the resulting solution gives a white precipitate with sulphide of ammonium (zinc).

PREPARATION.—Mixing hot aqueous solutions of sulphate of zinc and valerianate of sodium, evaporating at a gentle heat and crystallising. The crystals are washed with water until free from sulphate.

IMPURITIES.—Sulphate and butyrate of zinc from imperfect preparation.

TESTS.—Its solution in hot water is not precipitated by chloride of barium (no sulphate). It gives when heated with diluted sulphuric acid a distillate, which when mixed with the solution of acetate of copper, does not immediately affect the transparency of the fluid, but forms after a little time oily drops, which gradually pass into a bluish-white crystalline deposit (no butyrate).

DOSE.—½ to 4 gr.; the dose may be increased until some nausea is produced.

USES.—Valerianate of zinc has been supposed to combine the nervine tonic action of zinc with the antispasmodic effect of valerian; but it is much better to use valerian itself or its oil along with a salt of zinc, as the acid has no important physiological action. It is used in chorea, especially when occurring in hysterical persons, and should not be discontinued until symptoms of nausea begin to make their appearance. It is also employed in epilepsy and neuralgia.

U.S.P. Zinci Phosphidum. PHOSPHIDE OF ZINC. Zn_3P_2; 256·7.

CHARACTERS.—Minutely crystalline friable fragments, having a metallic lustre on the fractured surfaces, or a greyish black

powder permanent in the air having a faint odour and taste of phosphorus.

Solubility and Reactions.—Insoluble in water or alcohol, but completely soluble in hydrochloric or sulphuric acids with evolution of phosphoretted hydrogen.

Dose.—Not more than $\frac{1}{20}$ grain at first.

Uses.—Its action is similar to that of phosphorus, and it is used in place of it. Each grain contains nearly $\frac{1}{4}$ grain of phosphorus.

COPPER. Cu; 63·4.

Sources.—Its chief source is copper pyrites, which is a double sulphide of copper and iron.

General Reactions.—Ammonia throws down a pale blue precipitate of hydrate, which is soluble in excess, forming a deep blue solution. Potassium ferrocyanide gives a maroon red precipitate.

	Prepared from	By
Copper, B.P. . .	Copper pyrites .	Roasting with sand and coal.
Copper sulphate, B. and U.S.P.	Copper . . .	Heating copper or its oxide with sulphuric acid, dissolving in water and crystallising.
Copper nitrate, B.P.	Ditto . . .	Dissolving in nitric acid, evaporating and crystallising.
Copper acetate, B. and U.S.P.	Copper sulphate .	Precipitating with acetate of lead.

General Impurity.—Iron.

General Test.—If an aqueous solution of a copper salt be mixed with twice its volume of chlorine water, any iron present is converted into a ferric salt. If solution of ammonia be now added, cupric hydrate will fall as a precipitate of a pale blue colour, but is redissolved by excess, forming a deep blue solution. If iron be present, it will be precipitated by the ammonia and not redissolved.

Cuprum, Cu = 63·4. B.P. Copper.—Fine copper wire, about No. 25 wire gauge, or 0·02 inch.

Use.—To detect the presence of metals, as silver, mercury, and arsenic, by their being precipitated on its surface and forming a stain. It is employed in the preparation of sulphate and nitrate of copper and of spirit of nitrous ether.

B.P. Cupri Nitras. Nitrate of Copper, $Cu(NO_3)_2.6H_2O$.

Characters.—Deep blue prismatic crystals, very deliquescent, highly corrosive. With one-third of its weight of water it forms at a temperature below 70° F. (21·1° C.), tabular crystals; $Cu(NO_3)_2.6H_2O$. With a very little more water, added directly or absorbed from the air, it yields a styptic, caustic, corrosive fluid.

Reactions.—The diluted aqueous solution is only faintly acid to litmus; it gives the reactions of copper and a nitrate (p. 594).

Cupri Sulphas,[1] **B. and U.S.P.** SULPHATE OF COPPER. $CuSO_4.5H_2O$; 249·2.

CHARACTERS.—A blue crystalline salt, in oblique prisms.

PREPARATION.—*Vide* p. 674.

SOLUBILITY.—It is soluble in water, forming a pale blue solution which strongly reddens litmus.

REACTIONS.—The aqueous solution gives the reactions of copper and a sulphate.

DOSE.—As an astringent, $\frac{1}{4}$ to 2 grains; as an emetic, 5 to 10 grains.

B.P. Sulphate of Copper, Anhydrous. $CuSO_4$. Sulphate of copper deprived of its water by a heat of 400° F.

CHARACTERS.—A yellowish-white powder, which becomes blue when moistened with water.

ACTION.—Sulphate of copper has little or no action on the skin covered by epidermis, but when applied to the denuded skin it combines with the albuminous constituents of the tissues, forming an albuminate of copper. It thus acts as a mild **caustic**, and is an **astringent**. It has a similar astringent action on mucous membranes, and when swallowed in large doses it acts as a powerful **emetic**, like the sulphate of zinc, and in smaller doses as an astringent. Like sulphate of zinc, it probably exerts its action partly on the stomach itself and partly on the vomiting centre. Small doses absorbed into the blood appear to have a **tonic** action on some parts of the nervous system, and to exert an **astringent** action on mucous membranes. The copper is **excreted** by the mucous membrane of the intestine, by the bile, sweat, and kidneys. It is probable that its effect as an emetic when injected into the blood is partially due to the action it produces upon the stomach or intestines in the process of elimination (p. 39). Its action as an astringent upon other mucous membranes is probably due to a similar cause.

USES.—Sulphate of copper in substance is used as a mild caustic to the edges of sores, to repress exuberant granulations, both of ulcers and of trachoma, and as a styptic to arrest the blood from leech-bites. When mixed with honey it may be applied to the mouth in cancrum oris. In solution it may be applied to indolent ulcers, and to remove warts and parasitic skin-diseases, and as an injection into the nose to stop epistaxis. It is used as a wash to the eyes in ophthalmia, as an injection in gonorrhœa and leucorrhœa, and as a gargle in sore-throat. It is an efficient and rapid emetic in cases of narcotic poisoning, in phosphorus-poisoning, and in croup. It is a powerful astringent

[1] Oleate of copper is a useful application in cases of ringworm, applied night and morning. It is first prepared by drying a mixture of sulphate of copper (3 in 8 of water) and a solution of Castile soap (8 in 32), and may be applied in the form of ointment, 1 in 4 of petroleum cerate. It has also been used for indolent ulcers, warts, and corns.

in chronic diarrhœa, dysentery, and colliquative diarrhœa of phthisical patients. It is employed, like zinc, in chorea, epilepsy, and hysteria, but seems less useful than zinc. The nitrate has a similar action to the sulphate, but is more powerful as a caustic and styptic. It is a useful application to syphilitic sores on the tongue.

B.P. Test Solution of Ammonio-Sulphate of Copper. A test for arsenious acid, forming with it Scheele's green.

B.P. Subacetate of Copper of Commerce. Cu.CuO $(C_2H_3O_2)_2$. VERDIGRIS, AERUGO.—Used in solution as a test.

B.P. Test Solution of Acetate of Copper. USE.—In testing for butyric acid in valerianates.

U.S.P. Cupri Acetas. ACETATE OF COPPER. $Cu(CH_2)_2(CO{\cdot}OH)_2.H_2O$; 199·2.

CHARACTERS.—Deep green, prismatic crystals, yielding a bright green powder, efflorescent on exposure to air, odourless, having a nauseating metallic taste and an acid reaction.

TESTS.—If the aqueous solution of the salt be treated with hydrosulphuric acid until all the copper is precipitated, the filtrate should leave no residue on evaporation (alkalis, alkaline earths, or iron). If the aqueous solution be heated to boiling with solution of soda in excess, it will yield a filtrate which should not be clouded by hydrosulphuric acid (absence of lead and zinc).

USES.—Like sulphate of copper. Not used internally.

ARGENTUM. Ag; 108 B.P. (107·7 U.S.P.) Silver.

Argentum Purificatum. B.P. REFINED SILVER. Pure metallic silver.

IMPURITIES.—Gold, copper, and lead.

TEST.—If ammonia be added in excess to a solution of the metal in nitric acid, the resulting fluid exhibits neither colour nor turbidity.

PREPARATION.

Argenti Nitras.

Argenti Nitras, B. and U.S.P. NITRATE OF SILVER. LUNAR CAUSTIC.—$AgNO_3$; 169·7.

CHARACTERS.—In colourless tabular crystals, the primary form of which is the right rhombic prism; or in white cylindrical rods.

SOLUBILITY.—It is soluble in distilled water, and in rectified spirit.

REACTIONS.—The solution gives with hydrochloric acid a curdy white precipitate, which darkens by exposure to light, and is soluble in solution of ammonia. A small fragment heated on charcoal with the blowpipe, first melts, and then deflagrates, leaving behind a dull white metallic coating.

PREPARATION.—By dissolving silver in nitric acid, evaporating and crystallising.

It is obtained in rods by fusing the crystals in a capsule of platinum or

thin porcelain, and pouring the melted salt into proper moulds. Nitrate of silver must be preserved in bottles carefully stoppered.

Toughened nitrate of silver or '**toughened caustic**' is formed by adding 5 parts of nitrate of potassium to 95 parts of the nitrate of silver before fusion.

PREPARATIONS FOR WHICH NITRATE OF SILVER IS USED.

Argenti et Potassii Nitras.

Argenti Oxidum.

IMPURITIES.—Nitrate of potassium, metallic impurities.

TESTS.—Ten grains dissolved in two fluid drachms of distilled water give with hydrochloric acid a precipitate, which, when washed and thoroughly dried, weighs 8·44 grains. The filtrate, when evaporated by a water-bath, leaves no residue.

DOSE.—$\frac{1}{6}$ to $\frac{1}{2}$ grain.

ADMINISTRATION.—As an application to the eyes or injection it is used in solutions of various strengths, but an ordinary safe one is 2 grains to the ounce. When made into pill it must not be mixed with tannin, which reduces the silver to the metallic condition and becomes converted into gallic acid with evolution of carbonic acid gas. It is best made up into pill with kaolin and a very little tragacanth. As a draught it may be made up with dilute nitric acid, syrup, and mucilage.

U.S.P. Argenti Nitras Fusus. MOULDED NITRATE OF SILVER.

CHARACTERS.—A white, hard solid, generally in form of pencils or cones of a fibrous fracture, becoming grey or greyish-black on exposure to light in presence of organic matter.

PREPARATION.—Prepared by fusing together nitrate of silver 100 parts, hydrochloric acid 4 parts, and pouring into suitable moulds.

Argenti et Potassii Nitras, B.P. ; Argenti Nitras Dilutus, U.S.P. NITRATE OF SILVER AND POTASSIUM, B.P.; DILUTED NITRATE OF SILVER, U.S.P. Mitigated Caustic.

CHARACTERS.—White or greyish-white cylindrical rods or cones.

PREPARATION.—Prepared by fusing together nitrate of silver 1 part, with nitrate of potassium 2 parts, B.P.; 1 part, U.S.P.

SOLUBILITY.—It is freely soluble in distilled water, but only sparingly in rectified spirit.

REACTIONS.—The aqueous solution gives with hydrochloric acid a curdy white precipitate which darkens by exposure to light (silver); the filtrate from this mixture giving a yellow precipitate with perchloride of platinum (potassium), and evolving ruddy fumes when warmed with sulphuric acid and copper (nitrate).

GENERAL ACTION OF SILVER SALTS.—Soluble silver salts, such as the nitrate of silver, have a strong affinity for the cement by which epithelial or endothelial cells are united, and are, therefore, much used in staining microscopic preparations. They also unite with albumen, forming **albuminates** of silver. When applied to the **skin**, nitrate of silver produces a white

mark which rapidly becomes blackened by exposure to light, and the epidermis, either alone or with a slough varying in depth according to the strength of the application, is thrown off. Locally, it causes greater contraction of the **vessels** than other metals. In the **mouth** it has an unpleasant astringent taste, corrugates the mucous membrane, and acts as an irritant or caustic. In the **stomach**, in small doses, it acts as an astringent, and occasionally lessens vomiting, but in larger doses it acts as an irritant, and causes vomiting and symptoms of irritant poisoning (p. 396). In the **intestine** small doses are astringent, and, when absorbed from the blood, appear, like zinc or copper, to have a tonic action on some parts of the **nervous system.** When taken for a length of time it is apt to cause a livid discoloration of the skin. This discoloration appears to depend upon the amount of silver taken independently of the time during which its administration has been continued, so that it is advisable, when administering nitrate of silver to a patient, to inquire whether he has previously taken it or not, as the silver remaining in the system, together with that administered in the second instance, might cause a darkening of the skin which the quantity employed in the second course alone would not have produced. When taken for a long time, silver salts appear to produce fatty degeneration of the **tissues.** They are probably very slowly **eliminated** by means of albuminous secretions such as bile.

Uses.—Nitrate of silver may be applied to destroy parasitic fungi and remove tinea; to destroy the epidermis itself or epidermic structures such as warts, and to check the bleeding from leech-bites. In solution it relieves the itching of pruritus and of lichen. When sponged over the skin it hardens the epidermis and may prevent the formation of bed-sores. It is said to arrest vesication in herpes if painted over the surface as soon as the vesicles begin to form. It is also said that the pitting of small-pox is prevented by opening the vesicle and touching the surface beneath with a solution of the salt, or even by painting the solution over the skin. It has been recommended as a remedy in erysipelas, and is applied either by painting the strong solution over and beyond the inflamed surface, or by drawing a line with solid nitrate of silver upon the skin a little way beyond the margin of the inflammation. The alteration produced in the tissues underneath this line is said to prevent the extension of the inflammation beyond the limit thus formed. It is of little use in poisoned wounds, such as the bite of a mad dog (p. 347). Dilute solutions may be applied to the eye in tinea tarsi and conjunctivitis. In the mouth it may be used as an application to ulceration of the tongue, soft palate, or tonsils, and is often employed for this purpose on account of the readiness with which it can be applied; it is especially useful in follicular tonsillitis

and pharyngitis. In thus applying it care should be taken that it is well fixed in the holder, as otherwise a quick motion of the patient may break off the portable stick of nitrate of silver, which will probably fall into the pharynx, be swallowed, and may produce symptoms of irritant poisoning. The treatment of poisoning is to give common salt in order to form insoluble, and therefore inert, chloride of silver. Where the stick of nitrate of silver has been swallowed in substance this treatment has not always proved efficacious, and salt should therefore then be administered in combination with mucilaginous substances such as porridge and gruel, along with an emetic, so that the stick of silver may be at once evacuated from the stomach, while the mucilaginous envelope prevents it from doing any harm to the œsophagus on its way. It has been used to destroy the false membrane in croup, and as a useful application to the larynx in laryngeal phthisis. It may be applied either in solution of the strength of 30 grains to the ounce in laryngeal phthisis, by means of a brush, or in the form of lycopodium, which, after being dipped in the solution and then dried, may be blown by a curved tube into the larynx (cf. p. 480). It is sometimes used as an injection in gonorrhœa. Internally, it may be employed in irritable stomach, and also as an astringent in chronic diarrhœa and dysentery, and as a nervine tonic in chorea and epilepsy.

Argenti Oxidum, B. and U.S.P. OXIDE OF SILVER. Ag_2O; 231·4.

CHARACTERS.—An olive-brown powder, which at a low red heat gives off oxygen and is reduced to the metallic state.

SOLUBILITY AND REACTIONS.—It dissolves completely in nitric acid without the evolution of any gas, forming a solution which has the characters of nitrate of silver. 29 grains heated to redness leave 27 grains of metallic silver.

DOSE.—$\frac{1}{2}$ to 2 grains.

USES.—It has been used internally in neuralgic pain in the stomach, irritable dyspepsia, and pyrosis. Another drug not unfrequently given in similar affections is creasote; but creasote and oxide of silver are incompatible, as the former becomes oxidised at the expense of the silver oxide, and the mixture may undergo spontaneous combustion. It has been used in hæmorrhage from the stomach and lungs, and has been highly recommended in menorrhagia.

U.S.P. Argenti Cyanidum. CYANIDE OF SILVER. AgCN; 133·7.

CHARACTERS.—A white powder permanent in dry air, but gradually turning brown on exposure to light, odourless and tasteless.

SOLUBILITY.—It is insoluble in water or alcohol; insoluble in cold, but soluble in boiling nitric acid, with evolution of hydrocyanic acid; also soluble in water of ammonia and in solution of hyposulphite of sodium.

REACTIONS.—When heated the salt fuses, gives off cyanogen gas, and on ignition metallic silver is left.

OFFICINAL PREPARATION.

U.S.P.

Acidum Hydrocyanicum Dilutum.

U.S.P. Argenti Iodidum. IODIDE OF SILVER. AgI; 234·3.

CHARACTERS.—A heavy, amorphous, light-yellowish powder, unaltered by light if pure, but generally becoming somewhat greenish-yellow, without odour and taste.

SOLUBILITY.—It is insoluble in water, alcohol, diluted acids or in solution of carbonate of ammonium. Soluble in about 2,500 parts of stronger water of ammonia.

REACTIONS.—It is dissolved by an aqueous solution of cyanide of potassium and the resulting solution yields a black precipitate with hydrosulphuric acid or sulphide of ammonium (silver). If a small quantity of chlorine water be agitated with an excess of the salt, the filtrate acquires a dark blue colour on the addition of gelatinised starch (iodide).

DOSE.—1 to 2 grains.

USE.—It has been used instead of nitrate of silver in irritability of the stomach, dysmenorrhœa, and epilepsy.

Class II. GROUP IV.

MERCURY. Hg; 200.

Mercury is a liquid metal. It forms two series of compounds, viz. mercurous, in which it is univalent, e.g. Hg_2Cl_2; and mercuric, in which it is bivalent, e.g. $HgCl_2$. In constitution these salts are analogous to the cuprous and cupric salts.

GENERAL SOURCES.—The chief source is native sulphide or cinnabar.

Metallic mercury is prepared from this by roasting it either alone or with lime or iron.

GENERAL REACTIONS OF SALTS OF MERCURY.—They are all, either volatile, or decomposed by heat with the liberation of free mercury. The soluble salts are decomposed by stannous chloride; the mercuric salts giving first a white precipitate changing into black, and the mercurous salts a black one of finely divided mercury at once. Mercurous salts are most readily distinguished from mercuric salts by their reactions with alkaline carbonates, with ammonia, or with potassium iodide. The differences will be readily seen from the following table. The difference between the reactions of potash and ammonia with mercuric salts is noteworthy.

General Reactions of Salts of Mercury.

Reagent	Mercurous Salts	Mercuric Salts
Stannous chloride .	Black ppt. (finely divided mercury)	White ppt., turning black (calomel changing into mercury).
Caustic soda or potash	Black ppt. . .	Yellow ppt. (oxide).
Carbonates of sodium or potassium	White ppt. turning black	Red-brown ppt.
Ammonia . .	Black ppt. . .	White ppt. (double salt of mercury and ammon a).
Ammonium carbonate	White ppt. turning black	White ppt.
Potassium iodide .	Greenish-yellow ppt.	Bright scarlet ppt., soluble in excess either of mercuric chloride or of potassium iodide.

General Impurities.—Other metals, especially lead, arsenic, and antimony, may be present. But there is such an enormous difference between the activity of the mercurous and the mercuric salts, that the latter form the most important impurities of the former. Corrosive sublimate, for example, is so active that a slight trace of it as an impurity in calomel might cause a medicinal dose of the latter to produce poisonous effects.

General Test.—Mercuric salts are readily soluble in alcohol, and especially in ether, and also in a solution of sodium chloride, while mercurous salts are not. The presence of mercuric compounds as an impurity in mercurous preparations can be ascertained by shaking them with ether (B.P.), or with a solution of common salt (U.S.P.), filtering, and testing the filtrate for mercury. If no mercuric salt has been present, neither the ether nor salt solution will dissolve anything, and so the test will show the absence of mercury. When ether or alcohol is used, the absence of mercury may be ascertained by evaporating it and finding that no residue remains.

General Action.—Metallic mercury, mercurous salts, and mercuric salts all have actions differing from each other as far as their local effect is concerned, but agreeing together in their general result after absorption into the system. When applied locally to the skin, **mercury**, either in a state of vapour or when finely subdivided in the form of ointment, will pass through the epidermis without exciting any local irritation, and be absorbed into the circulation, where it will produce the general effects of the drug. Taken in the form of vapour into the lungs, it will have a similar action. The **mercurous salts** are also absorbed in the same way as metallic mercury. They have a slightly more stimulating effect than it, but do not produce the same intense irritation that the mercuric salts cause. The **mercuric salts** unite with albumen, forming **albuminates**. They have little action on the epidermis, but when applied to the denuded skin, or to a mucous membrane, they precipitate the albumen, and, when used in a concentrated form, produce a slough. When swallowed, they cause the symptoms of gastro-enteritis produced by other irritant poisons, but these may be quickly succeeded by

the symptoms of special mercuric poisoning from the absorption of the substance into the circulation (cf. p. 398).

The general effects on the body which are produced alike by mercury and its salts are termed **mercurialism.**

The first symptoms produced by mercury, however it is applied, are almost always connected with the alimentary canal, and more especially the **mouth.** A metallic unpleasant taste is observed in the mouth, along with a feeling of heat; the saliva is somewhat increased and the breath has a most unpleasant smell. The teeth feel sticky, as if their edges were glued together with some adhesive substance, when the patient tries to separate them; they feel as if they were longer than usual. The gums are red and swollen and tender, and chewing is painful. The tongue is covered with a thick coating, and the appetite is small. The **medicinal administration** of mercury is generally **stopped** when the gums become sore and salivation begins. In children salivation occurs with difficulty, and mercury may be discontinued when the breath becomes fœtid or the previously healthy stools become green and offensive. When the administration of mercury is continued the symptoms increase; the gums become still more inflamed, their edges are covered with a white sticky substance, and they bleed on the slightest touch; the teeth become loosened in their sockets, and the **salivation** becomes still greater.

In still worse cases ulcers form on the gums and inside the cheeks, the tongue itself becomes swollen so that articulation becomes difficult, mastication is so painful as to be nearly impossible, the fœtor of the breath is insupportable, and the saliva pours from the mouth in great quantities.

Along with these symptoms there is a certain amount of **fever,** which, indeed, sometimes is present before any local symptoms have appeared. There is general depression, chilliness, and even rigors, followed by a rise of temperature, a feeling of heat, thirst, loss of appetite, quick pulse, weight or pain in the epigastrium, nausea, belching, vomiting, and purging, sometimes bloody motions, or more rarely constipation. These symptoms last several days and then decrease, sweating occurring at the same time, or salivation if the fever has preceded it. Mercurial fever occurs most readily after a lengthened application of blue ointment.

When the administration of mercury is stopped the symptoms decrease, though in the case of broken-down individuals necrosis of the jaw, and even death, has occurred.

Occasionally it has happened that even healthy individuals, instead of recovering after profuse salivation, have become permanently dyspeptic.

These symptoms appear in adults, generally with great regularity, when a similar quantity of mercury has been taken in a similar time, though the effect is modified by various conditions, as age, sex, the presence of disease, &c.

When persons are exposed for a long time to the fumes of mercury, and the metal is thus taken in in very small quantities for a lengthened period, a different effect is sometimes produced. This is called **mercurial cachexia.** In this condition the appetite is lost, the gums become livid and bleed easily, the breath is fœtid, the tonsils and fauces become congested or even ulcerated, and a tendency to diarrhœa is often present. In bad cases vomiting and purging generally occur.

The lips become pale, the complexion earthy, the person becomes emaciated, the hair sometimes falls out, the muscles become weak and small. The person is easily affected by changes of weather; there is a tendency to fainting, uneasiness, and anxiety; the pulse and respiration become quick; the pulse is also small and intermittent; and palpitation becomes very troublesome. The intellect is dull, and rheumatic pains are felt in the muscles of the extremities, more rarely in those of the trunk.

These symptoms go on increasing, and new ones also appear. **Mercurial tremors** occur in the muscles, beginning generally in the upper extremities, and gradually extending till the patient cannot execute any movement, and the speech itself becomes stammering.

Mercurial paralysis of muscles or groups of muscles occasionally occurs. Generally this is confined to the muscles of the upper extremities, but sometimes affects other muscles, such as those of the larynx, causing mercurial aphonia. These paralyses generally occur in the later stages of mercurial erethism, and rarely occur before the other symptoms.

The **mental qualities** become also affected. Ill-humour, irritability, melancholy, and fear of death occur in some persons, and in others, though very rarely, idiocy, and still more rarely, furious mania. In some instances epilepsy has been observed.

Mercury in the form of organic compounds appears to have a special action on the **brain.** The symptoms are those of impairment of the special senses, sight, taste, hearing, of motor power, and of the cerebral functions. Two chemists who were engaged in the preparation of mercuric methide during three months, suffered from weakness and dimness of vision, and one of them from some soreness of the gums, nausea, and vomiting. At the end of this time the symptoms became much worse, deafness and numbness came on, and were succeeded by a semi-comatose condition with great restlessness. In the one who had not previously suffered from soreness of the gums, this now appeared, along with fœtor of the breath; the urine was albuminous, Cheyne-Stokes' breathing was observed, the evacuations were passed involuntarily, and he died comatose a fortnight after the symptoms became severe. Sensibility was retained nearly to the last. In the other patient, impaired sensation, loss of power to direct movement, and muscular feebleness were succeeded by

involuntary passage of evacuations, an idiotic condition of restlessness, and violent muscular movements, especially when he was touched. After remaining in an idiotic state for a year he died of pneumonia.

The action of mercury may be **modified** by sex, age, or idiosyncrasy. Women, as a rule, are more easily affected than men, whilst children may take mercury in considerable quantities without showing any symptom of salivation. In certain persons large quantities of mercury may be administered for a length of time without producing much more effect than in children, but in others exceedingly injurious results may follow very minute doses. A case of salivation from as little as a grain and a half of calomel has been recorded, and from one-eightieth of a grain of corrosive sublimate. In typhus it is very hard to produce salivation, but in persons suffering from Bright's disease, although mercury may be useful as a purgative, it requires to be given with caution, on account of the violent effects which may follow even small doses.

Mercury combines with **albumen**, and forms albuminate of mercury, which is insoluble in water, but is easily soluble in excess of albumen or in chloride of sodium. This compound may be formed in the stomach or intestines, and a compound of mercuric oxide with albumen is probably the form under which mercury, however administered, circulates in the blood. When taken into the **stomach**, mercuric salts are powerful irritants, and, when given in large quantities, cause gastro-enteritis, vomiting, and purging, with bloody stools. Finely divided metallic mercury and mercurous salts are less irritating, and act simply as purgatives.

A good deal of discussion has arisen regarding the action of mercury on the **liver.** It has long been ranked as a cholagogue, and there can be no question whatever that mercury and its compounds are very beneficial in cases of so-called bilious disorder characterised by feelings of laziness and apathy, inability to think, dislike of exertion, not unfrequently combined with irritability of temper, deranged digestion, and slight yellowish tinge of the eyes. When bile was supposed to be formed in the blood, and to be only excreted by the liver, the beneficial effect of mercury was attributed to a stimulating action on the liver, whereby it increased the rapidity of the secretion, and thus removed the bile more quickly from the blood. But it was found on experiment by Dr. Scott that mercury does not increase the rapidity of the biliary secretion, and this result was confirmed by a committee of the British Medical Association, the chief members of which were Hughes Bennett, Rutherford, and Gamgee, and also by later experiments made by Rutherford, Vignal, and Dodds. As we now know that bile is formed by the liver, and not merely separated from it by the blood, we can understand

that the real action of mercury as a cholagogue consists, not in its stimulating the liver to form more bile, but in removing more readily from the body the bile which is already present in excess. It appears to perform this function by stimulating the upper part of the small intestine, and thus causing the evacuation of the bile before time has been allowed for its reabsorption. For the liver does not merely form bile, it also excretes bile which has been previously formed and reabsorbed from the intestine. The bile may thus serve several times over. It is formed, passes from the liver into the duodenum, is reabsorbed, and carried by the portal blood to the liver, where it is again excreted and poured out through the bile-duct a second time (p. 404). Part of it, however, is carried down the intestine, decomposed, and evacuated, and to supply the place of this a certain amount of new bile is constantly being formed, which is poured into the intestine along with the old. It is evident that any drug which acts upon the lower part of the intestine will have little power to remove the bile, as this will have undergone absorption already in the upper part of the digestive tract. But any drug acting upon the duodenum will cause the bile to be rapidly moved on and its absorption to be prevented. More especially will this be the case if the cholagogue be combined with a saline purgative, which, by causing a profuse secretion of watery fluid, will wash the bile out. This action on the upper part of the small intestine is probably possessed by mercury, and the reasons for this supposition are: (1) that it is so beneficial in bilious disorders; (2) that it does cause the appearance of bile in the stools, for Buchheim has found by analysis that the green stools which occur after purgation by calomel actually owe their colour to bile; and (3) that in the stools passed after mercurial purgatives, leucin and tyrosin, the products of pancreatic digestion, have been found, showing the rapid peristalsis produced. Mercury acts as a **disinfectant of the intestinal contents.**

After the absorption of mercury into the **blood**, it is said, in small doses, to increase the number of blood-corpuscles; in larger doses, however, it produces anæmia, but how far these results are dependent upon the improvement or disturbance of the digestion, and how far upon the action of the mercury itself upon the blood, has not been ascertained. Albuminate of mercury, when added to blood out of the body, gradually destroys the corpuscles.

Mercury appears to have the power of causing absorption of **fibrinous exudations**, for the fibrinous adhesions observed in syphilitic iritis have been seen to disappear as the patient was brought under the influence of mercury. When mercury is used for a long time, it appears to lessen greatly the force of the pulse, and large doses of mercuric preparations, when brought into contact with a frog's **heart**, will arrest its pulsations immediately.

The **respiration** is affected in persons who have been taking too much mercury, and becomes laboured and accompanied by a feeling of constriction. The **temperature** is rarely affected, excepting secondarily, in consequence of local inflammations which the mercury may excite, although sometimes mercurial fever (p. 682) precedes any marked local change.

Mercury is **excreted** by the saliva, bile, urine, sweat, and milk. The **salivation** which it produces is probably due in part to reflex excitement of the salivary glands by the irritation of the tongue, but it is no doubt also in part due to irritation of the nerves of the gland, or of the gland-structure itself, by the mercury. The **urine** is said to be somewhat increased, and it is stated that the addition of a little mercury to digitalis and squill greatly increases the diuretic action of these drugs. Calomel has an undoubted diuretic action, and it has been suggested that it owes this action to the increase of urea in the blood, produced by part of the salt being changed into mercuric chloride, which acts as an hepatic stimulant (cf. p. 432).

Hydrargyrum. B. and U.S.P. MERCURY. Hg; 200 B.P. 199·7 U.S.P.

CHARACTERS.—A metal, fluid at common temperatures, brilliantly lustrous, and easily divisible into spherical globules.

REACTION.—Volatilises at a heat below that of visible redness, leaving no residue.

PREPARATIONS CONTAINING MERCURY.[1]

B.P.	U.S.P.
I. In the metallic state.	
(9)	(7)
Hydrargyrum.	Hydrargyrum.
Emplastrum Ammoniaci cum Hydrargyro (1 in 5).	Emplastrum Ammoniaci cum Hydrargyro.
Emplastrum Hydrargyri (1 in 3).	Emplastrum Hydrargyri.
Hydrargyrum cum Creta (1 in 3).	Hydrargyrum cum Creta.
Linimentum Hydrargyri (*v.* p. 516) (1 in 6).	
Pilula Hydrargyri (*v.* p. 522) (1 in 3).	Massa Hydrargyri.
Suppositoria Hydrargyri (1 in 6).	
Unguentum „ (1 in 2).	Unguentum Hydrargyri.
„ „ **Compositum** (1 in 4½).	„ „ Compositum.
II. Oxidised.	
(5)	(4)
Hydrargyri Oxidum Flavum.	Hydrargyri Oxidum Flavum.
„ „ **Rubrum.**	„ „ Rubrum.
Lotio Hydrargyri Flava.	
„ „ **Nigra.**	
	Unguentum Hydrargyri Oxidi Flavi
Unguentum Hydrargyri Oxidi Rubri.	„ „ „ Rubri
III. Sulphuretted.	
	(1)
None.	Hydrargyri Sulphidum Rubrum.
IV. As Mercurous Chloride.	
(3)	(3)
Hydrargyri Subchloridum.	Hydrargyrum Chloridum Mite.
Pilula Hydrargyri Subchloridi Composita (*vide* p. 522).	Pilulæ Antimonii Compositæ (*vide* p. 523).
	Pilulæ Catharticæ Compositæ (*vide* p. 523).
Unguentum Hydrargyri Subchloridi.	

[1] Altered from the *United States Dispensatory*, p. 773.

PREPARATIONS CONTAINING MERCURY—*continued.*

V. **As Mercuric Chloride.**

B.P. (4)	U.S.P. (3)
Hydrargyri Perchloridum.	Hydrargyri Chloridum Corrosivum.
Hydrargyrum Ammoniatum.	Hydrargyrum Ammoniatum.
Liquor Hydrargyri Perchloridi.	
Unguentum Hydrargyri Ammoniatum.	Unguentum Hydrargyri Ammoniati.

VI. **Combined with Iodine.**

(3)	(3)
Hydrargyri Iodidum Rubrum.	Hydrargyri Iodidum Rubrum.
	,, ,, Viride.
Liquor Arsenii et Hydrargyri Iodidi.	Liquor Arsenii et Hydrargyri Iodidi.
Unguentum Hydrargyri Iodidi Rubri.	

VII. **Combined with Cyanogen.**

	(1)
None.	Hydrargyri Cyanidum.

VIII. **Oxidised and combined with Acids.**

(5)	(4)
Hydrargyri Persulphas.	
	Hydrargyri Sulphas Flava.
Liquor Hydrargyri Nitratis Acidus.	Liquor Hydrargyri Nitratis.
Oleatum Hydrargyri.	Oleatum Hydrargyri.
Unguentum Hydrargyri Nitratis.	Unguentum Hydrargyri Nitratis.
,, ,, ,, Dilutum.	

IMPURITIES.—Other metals.

TESTS.—The presence of other metals is ascertained by their being left behind as a residue when the mercury is volatilised. It is indicated by the formation of a grey scum or dust on the surface of the metal after exposure to air, and by the mercury forming globules which are not spherical but elongate to a tail when allowed to run over a piece of paper. They are also recognised by shaking the mercury in a perfectly dry bottle, when a grey powder will be formed if they are present.

On boiling 5 grms. of distilled water with 5 grms. of mercury and 4·5 grms. of hyposulphite of sodium in a test-tube for a minute, the mercury should not lose its lustre nor acquire more than a slightly yellowish shade (absence of more than a trace of other metals, U.S.P.).

PURIFICATION.—Other metals may be separated by distillation, or by mixing the mercury with strong sulphuric acid and letting it stand in the cold for twenty-four hours. The other metals will be converted into sulphates, but mercury is only attacked by sulphuric acid when it is aided by heat. The mercury is then washed with water to remove the sulphates, and dried with blotting-paper. Mercury is freed from dust and mechanical impurities by pressing it through chamois leather or filtering it through a paper filter in the apex of which several small holes have been made with a needle or pin.

USES.—Metallic mercury in mass has no action whatever on the body. As much as a pound has been taken without producing any physiological effect. Such a dose as this is sometimes given in cases of intestinal obstruction in the hope that the weight of the mercury may carry the obstruction before it. The theory of its action formerly held was purely mechanical: that the mercury passed from the stomach to the intestines and meeting with the obstruction drove it on; but latterly Traube

has supposed that the mercury remains chiefly in the stomach, and by pulling on it excites the intestines reflexly to peristaltic action. Whatever the correct theory may be, however, it is certain that the mercury does not always stay in the stomach, but does get down into the intestine, and consequently some precautions must be observed in its administration, and it is never given except when all other measures fail. The precautions are not to give it in cases of intussusception, as it may very probably render this worse; nor in cases where the intestine is considerably inflamed, as the tissues being weak are then easily torn; nor in hernia, as better means, viz. external means, can be employed.

Hydrargyrum cum Creta, B. and U.S.P. MERCURY WITH CHALK.

PREPARATIONS.—By rubbing up chalk (2) and mercury (1) together, B.P. By rubbing up mercury (38), chalk (50), and sugar of milk (12) together, moistening them with a mixture of equal parts of ether and alcohol, U.S.P.

CHARACTERS.—A powder of light-grey colour; free from grittiness; insoluble in water; partly dissolved by diluted hydrochloric acid, leaving the mercury in a finely-divided state.

IMPURITY.—Mercuric oxide.

TEST.—The solution formed with hydrochloric acid is not precipitated by the addition of chloride of tin.

DOSE.—3 to 8 grains.

USES.—It has been much recommended by Ringer as a remedy in many diseases both of adults and of children. In simple tonsillitis, or the inflamed throat of scarlatina, or in mumps, he recommends a third of a grain every hour, and the same dose three or four times a day will, he says, clean the tongue, remove the disagreeable taste from the mouth, and improve appetite and digestion in the dyspepsia occurring in chronic disease or commencing convalescence. A similar dose will cut short an attack of jaundice, with vomiting and pale stools, occurring in nervous persons after exposure to cold, fatigue, or excitement; and half a grain thrice a day will restore the colour to the stools and remove the dyspepsia in patients suffering from acidity, flatulence, and vomiting in the morning. Diarrhœa in children, accompanied by pale, offensive motions, or by muddy, or green-coloured, or curdy stools, whether accompanied by sickness or not, is successfully treated by similar doses of this remedy. It may also be used to produce the general action of mercury combined with opium or Dover's powder.

B.P. Pilula Hydrargyri. MERCURIAL PILL; BLUE PILL (p. 522). 3 grs. contain 1 of mercury.

DOSE.—3 to 8 grains.

U.S.P. Massa Hydrargyri. BLUE MASS; BLUE PILL.—Mercury (33), powdered liquorice (5), althæa (25), glycerin (3), honey of rose (34). 3 grs. contain 1 of mercury.

USES.—Blue pill may be given either for its local action upon the intestines or to produce the action of mercury upon the system. This pill is one of the most effectual remedies for the condition usually termed biliousness. The patient complains of feeling

dull, heavy, and often sleepy, suffers from occasional headache, has little appetite, and occasionally feels sick. The complexion is often of a dirty-yellow, muddy colour, and the white of the eyes likewise. The use of blue pill in such conditions was recommended by Mr. Abernethy. Five grains of blue pill are given overnight and a draught of salts and senna in the morning. This is very effective, but the disadvantage of it is said to be that the bilious state is more apt to return, and that when a patient has once become habituated to the use of mercurials no other medicine will do instead.

It is one of the best preparations for producing **mercurialism**: 5 grains with $\frac{1}{2}$ grain of opium are given in the morning, and 5 or 10 also with $\frac{1}{2}$ grain of opium in the evening.

The addition of a small quantity of blue pill to digitalis and squill sometimes increases their efficacy in cases of cardiac disease.

Unguentum Hydrargyri, B. and U.S.P. OINTMENT OF MERCURY, B.P.; MERCURIAL OINTMENT, U.S.P.—Contains 1 lb. each of mercury and prepared lard. As this would be too soft, 1 oz. of prepared suet is added.

PREPARATIONS.

Linimentum Hydrargyri (p. 516).
Suppositoria Hydrargyri.
Unguentum Hydrargyri Compositum.

USES.—It may be used either for its general or its local action. When employed to produce the **general action** of mercury in the system, it is rubbed into some part of the body where the skin is thin, as the armpits or the sides of the thighs. If it is rubbed in by another person, and not by the patient himself, it is advisable to protect the operator's hand by a piece of bladder soaked in oil, in order to prevent absorption through the palm. In cases of congenital syphilis, a piece of mercurial ointment, the size of the thumb-nail (half a drachm to one drachm), may be put upon a flannel roller, and bound round the child's belly.

It has been applied **locally** in inflammation of the skin, as erysipelas; of the veins in phlegmasia dolens; or of the genital organs, as in ovaritis, orchitis, and indurated testicles.

B.P. Suppositoria Hydrargyri. MERCURIAL SUPPOSITORIES.—Each contains 60 grs. of ointment of mercury, benzoated lard and white wax each 20 grs., oil of theobroma 80 grs.

USES.—They are employed where we wish to produce mercurial action without the risk of interfering with the digestion.

B.P. Unguentum Hydrargyri Compositum. COMPOUND OINTMENT OF MERCURY.—Contains mercurial ointment (6), yellow wax (3), olive oil (3), and camphor ($1\frac{1}{2}$).

The compound ointment is used to cause absorption of effusion or thickening around joints in cases of disease or injury after the inflammation has subsided. It ought to be combined with pressure and rest.

B.P. Linimentum Hydrargyri. LINIMENT OF MERCURY.—*Vide* p. 516.

Used for similar purposes as the plaster or ointment. It is more irritating than either, on account of the ammonia it contains. It is said to cause salivation more readily than mercurial ointment, as the camphor and ammonia with which it is mixed assist its absorption.

Emplastrum Hydrargyri, B. and U.S.P. Mercurial Plaster.

Preparation.—Rub mercury with olive-oil, and sulphur B.P. or resin U.S.P., and add lead plaster to give it consistency. Sulphur and resin are used to extinguish the globules of mercury, i.e. make them so small as to be invisible.

Emplastrum Ammoniaci cum Hydrargyro, B. and U.S.P. Ammoniacum and Mercury Plaster, B.P.; Ammoniac Plaster with Mercury, U.S.P.

Preparation.—B.P. By rubbing mercury 3 oz. with warm olive-oil 1 fl. dr., and sulphur 8 grs. until the globules of mercury are no longer visible, then adding melted ammoniacum 12 oz. and mixing. U.S.P. Mercury 180 is extinguished with sulphur 1 and olive oil 8 as in the B.P. process. Ammoniacum 720 is digested with diluted acetic acid 1,000, strained, evaporated until it hardens on cooling. It is then added while hot to the mercury, and mixed. Then enough lead plaster previously melted is added to make up to 1,000 parts.

Both plasters are used to promote the absorption of glandular enlargements, buboes, nodes, and are applied over the liver in chronic enlargement and induration. Emplastrum hydrargyri is useful also in sycosis, lupus, and other deep-seated infiltrations of the skin.

B.P. Hydrargyri Persulphas. Persulphate of Mercury. $HgSO_4$.

Characters.—A white crystalline heavy powder.

Preparation.—Heat mercury 20 oz. with sulphuric acid 12 fl. oz. in a porcelain vessel, stirring constantly until the metal disappears, then continue the heat until a dry white salt remains.

Reactions.—It is rendered yellow by affusion with water, the subsulphate being formed. Entirely volatilised by heat.

Preparations in which Sulphate of Mercury is used.

Hydrargyri Perchloridum. Hydrargyri Subchloridum.

U.S.P. Hydrargyri Subsulphas Flavus. Yellow Subsulphate of Mercury. $Hg(HgO)_2SO_4$; 727·1.

Characters.—A heavy lemon-yellow powder, permanent in the air, odourless and almost tasteless.

Solubility.—It is insoluble in water or in alcohol, but soluble in nitric or hydrochloric acid.

Reactions.—When heated the salt turns red, becoming yellow again on cooling. At a red heat it is volatilised without residue, evolving vapours of mercury and of sulphurous acid.

Tests.—As it is a mercuric oxysulphate, it should be soluble in 20 parts of hydrochloric acid without residue (no mercurous salt).

Uses.—The yellow oxysulphate has been used under the name of Turpeth mineral as an errhine in chronic ophthalmia. It is a prompt emetic, and is sometimes preferred to other emetics in croup, as it is quick and certain, and does not produce depression nor purging. The dose for a child two years old is 2–5 grains (0·13–0·33 gm.), repeated in fifteen minutes if necessary. It may also be used as an alterative.

Hydrargyri Subchloridum, B.P.; Hydrargyri Chloridum Mite, U.S.P. SUBCHLORIDE OF MERCURY, HgCl, B.P.; MILD CHLORIDE OF MERCURY, Hg_2Cl_2; 470·2, U.S.P. CALOMEL.

CHARACTERS.—A dull-white, heavy and nearly tasteless powder, rendered yellowish by trituration in a mortar.

SOLUBILITY.—It is insoluble in water, spirit, or ether.

REACTIONS.—It is very heavy, and can be distinguished by its weight from almost every other white powder. Its weight is noticed more distinctly by giving the bottle an up-and-down shake. Digested with solution of potash it becomes black (mercurous oxide); and the clear solution, acidulated with nitric acid, gives a copious white precipitate with nitrate of silver (chloride). Contact with hydrocyanic acid also darkens its colour.

PREPARATION.—Calomel is prepared by rubbing up mercury with sulphate of mercury moistened with water till globules are no longer visible, adding sodium chloride, mixing the whole by trituration, and subliming the mixture into a large chamber.

The mercury and mercuric sulphate form mercurous sulphate, and this, with sodium chloride, forms calomel and sulphate of sodium, $HgSO_4 + Hg + 2NaCl = Hg_2Cl_2 + Na_2SO_4$.

When the calomel is sublimed into a small receiver it forms a thin crystalline crust which adheres to the sides, but when sublimed into a large chamber, as directed in the B.P., it falls as a powder on the floor. As some corrosive sublimate is often formed, the powdered calomel is washed with water till all the sublimate is removed, as shown by the water no longer giving a precipitate with ammonium sulphide.

It is then dried under 212° F., and kept in a well-stoppered and dark bottle.

ADULTERATIONS.—Chalk, sulphate of calcium, sulphate of barium, carbonate of lead, corrosive sublimate.

TESTS.—It is entirely volatilised by a sufficient heat (no earthy impurities). Warm ether which has been shaken with it in a bottle leaves, on evaporation, no residue (no corrosive sublimate).

DOSE.—$\frac{1}{2}$ grain to 5 grains.

PREPARATIONS IN WHICH SUBCHLORIDE OF MERCURY IS USED.

B.P.	DOSE.
Lotio Hydrargyri Nigra (3 grains to 1 fluid ounce)	
Pilula Hydrargyri Subchloridi Composita (1 part in 5, v. p. 522).	5–10 grs.
Unguentum Hydrargyri Subchloridi, Calomel Ointment (with prepared lard) } (1 part in $6\frac{1}{2}$, nearly)...........	

U.S.P.

Pilulæ Antimonii Compositæ (p. 523).
Pilulæ Catharticæ Compositæ (p. 523).

Pilula Hydrargyri Subchloridi Composita, B.P. PILULÆ ANTIMONII COMPOSITÆ, U.S.P.; COMPOUND PILL OF SUBCHLORIDE OF MERCURY, B.P.; COMPOUND PILLS OF ANTIMONY, U.S.P. COMPOUND CALOMEL PILL. PLUMMER'S PILL (p. 522).

B.P. Lotio Hydrargyri Nigra. BLACK MERCURIAL LOTION. BLACK WASH. Consists of half a drachm of calomel mixed with half a pint of lime-water. It contains suboxide of mercury.

USES.—Calomel may be employed as a dusting powder to remove condylomata from the skin, and condylomatous patches from the tongue, throat, and larynx; it is also recommended in the following powder—calomel, six parts, boric acid, three parts, salicylic acid one part.[1] As an ointment it may be applied to

[1] *Philadelphia Medical Reporter*, June 14, 1884.

relieve the itching in pruritus ani and pruritus scroti, and pityriasis of the scalp, and to heal strumous sores and lupus in children. In pruritus pudendi it is also of service, though not quite so much as in the other cases (Ringer). It should not be applied in large quantities, lest so much of it be absorbed as to cause its physiological action. Calomel ointment ($\frac{1}{2}$ to 1 drachm to the ounce) is useful in the treatment of small patches of vesicular eczema; and in psoriasis Rochard's ointment, which contains one part of iodine and one and a half part of calomel to seventy parts of simple ointment, is beneficial in some cases. Black wash is a good application to varicose ulcers, and is used as an application to syphilitic ulcerations, as a wash to the mouth in syphilitic sore-throat and in cancrum oris.

Internally calomel may be given in cases of biliousness, and followed by a saline purgative in the same manner as is recommended under 'Blue Pill.' In some cases of diarrhœa it is very useful in combination with opium (p. 106).

It may also be used to produce the general action of mercury in syphilitic patients, and for this purpose may either be given internally, in combination with opium, or applied to the skin in the form of calomel fumigations (p. 471).[1]

The compound pill of subchloride of mercury may be used in cases of biliousness, gout or rheumatism.

Calomel is a useful diuretic in some cases of dropsy (pp. 432 and 686), especially when due to heart-disease. It must be given in doses of 4 or 5 grains, repeated when necessary, salivation being prevented by a chlorate of potassium gargle, and diarrhœa by small doses of opium.[2]

Hydrargyri Perchloridum, B.P.; Hydrargyri Chloridum Corrosivum, U.S.P. PERCHLORIDE OF MERCURY, B.P.; CORROSIVE CHLORIDE OF MERCURY, U.S.P. $HgCl_2$; 270·5.

CHARACTERS.—In heavy colourless masses of prismatic crystals, possessing a highly acrid metallic taste.

PREPARATION.—By mixing mercuric sulphate with sodium chloride and subliming into a small chamber. To prevent the formation of any calomel some peroxide of manganese is added.

SOLUBILITY.—It is more soluble in alcohol, and still more so in ether, than in water.

REACTIONS.—Its aqueous solution gives the reactions of mercuric salts (p. 681) and of a chloride (p. 594).

DOSE.—$\frac{1}{16}$ to $\frac{1}{8}$ grain. In cholera and summer diarrhœa this dose may be given every quarter of an hour, half-hour, or hour.

A solution of 1 in 500 or 1 in 1,000 (about $\frac{1}{2}$ grain in 1 oz. or the liquor of the B.P.) may be used as an antiseptic lotion or for a spray in diphtheria.

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[1] Mercurous tannate has been used in doses of one grain and a half twice or thrice a day in syphilis. It is said to be efficient, and yet neither to interfere with the digestion, nor to cause any stomatitis. *Zeitsch. f. Therapie*, 2, 1884.

[2] Jendrássik, *Deutsch. Archiv f. klin. Med.*, vol. xxxviii. p. 499.

OFFICINAL PREPARATIONS.

B.P.	DOSE.	U.S.P.
Liquor Hydrargyri Perchloridi	½–2 fl. drm.	None.

Lotio Hydrargyri Flava (18 grs. in 10 fl. oz.).

Used in preparing.—Hydrargyri Iodidum Rubrum; Hydrargyrum Ammoniatum.

B.P. Liquor Hydrargyri Perchloridi. SOLUTION OF PERCHLORIDE OF MERCURY.—Contains ½ grain of perchloride of mercury in 1 oz. of water, with ½ grain of ammonium chloride to keep it in solution and prevent precipitation.

USES.—When mixed with **albumen**, corrosive sublimate precipitates it, forming a mercuric albuminate. It is one of the most powerful **antiseptics** known (p. 95). It may be applied (in the strength of 2 grains to the ounce of water) to the skin to destroy vegetable and animal parasites present upon it, such as the fungus in pityriasis versicolor, in sycosis and favus, the acarus in scabies and the pediculus pubis. It is the most powerful remedy for the removal of the pigment in chloasma, and may be applied in a lotion of bichloride of mercury 2 grains, tincture of benzoin half a drachm, and 1 ounce of almond emulsion. For the rapid removal of pigment Hebra used a solution of 5 grains to the ounce of alcohol and water, and applied it by means of compresses for 4 hours, so as to raise a blister; the relief, however, is not permanent, since pigmentation returns. The danger of absorption must be considered, so that it is unwise to apply the treatment to large surfaces. It is useful in allaying the itching of pruritis scroti and pudendi, prurigo, and urticaria. It may be employed as a wash in ophthalmia (p. 216), as a gargle in syphilitic sore-throat, as a spray in diphtheria (p. 692), and as an injection in gonorrhœa, gleet, and leucorrhœa, or for the uterus and vagina in puerperal conditions. When swallowed in strong solution it sometimes causes an **irritant poisoning** (p. 395 *et seq.*); and if this should pass off, it may be succeeded by intense salivation due to the absorption of the drug. The treatment in such cases is to give albuminous substances, such as white of egg or milk, in order to form mercuric albuminate in the stomach, and thus prevent its irritant action on the mucous membrane. If the irritation which the drug itself produces is not sufficient to cause vomiting, the stomach should be emptied by an emetic or the stomach-pump, in order to prevent digestion and absorption of the mercuric albuminate and the poisoning which might occur from its absorption. In small and frequently-repeated doses it is useful in the dysenteric diarrhœa of adults or children and in cholera, its utility probably depending, to a great extent at least, on its antiseptic power, which is not destroyed, like that of other antiseptics, by considerable admixture with organic matter, such as the fæcal contents of the intestine (p. 106). After its absorption it has the same effect as the other salts of mercury, and may be used for this purpose in syphilitic cases.

B.P. Lotio Hydrargyri Flava. YELLOW WASH.

PREPARATION.—By mixing 18 grs. of corrosive sublimate with half a pint of lime-water.

USES.—It is used as a stimulating application to syphilitic sores in cases where the black wash is not sufficiently powerful.

Hydrargyri Oxidum Flavum, B. and U.S.P. YELLOW OXIDE OF MERCURY. HgO; 215·7.

CHARACTERS.—A yellow powder readily dissolved by hydrochloric acid, yielding a solution which, with solution of ammonia, gives a white precipitate. It is entirely volatilised when heated to incipient redness, being resolved into oxygen gas and the vapour of mercury.

PREPARATIONS.

U.S.P.

Unguentum Hydrargyri Oxidi Flavi (1 in 10 of Unguentum).

B. AND U.S.P.

Oleatum Hydrargyri (yellow oxide 10, oleic acid 90, parts).

USES.—The oleate of mercury acts beneficially in ringworm, and may be used for inunction in cases of syphilis in doses of 10 to 30 drops.

Hydrargyri Oxidum Rubrum, B. and U.S.P. RED OXIDE OF MERCURY. HgO; 215·7.

CHARACTER.—An orange-red powder.

SOLUBILITY AND REACTIONS.—It is readily dissolved by hydrochloric acid, yielding a solution which, with caustic potash added in excess, gives a yellow precipitate, and with solution of ammonia a white precipitate.

PREPARATION.—Triturate nitrate of mercury and metallic mercury together, and heat until nitrous fumes cease to be given off. $Hg(NO_3)_2 + Hg = 2HgO + N_2O_4$.

IMPURITY.—Undecomposed nitrate.

TEST.—Entirely volatilised by a heat under redness, being at the same time decomposed into mercury and oxygen. If this be done in a test-tube, no orange vapours are perceived.

PREPARATIONS.

B. AND U.S.P.

Unguentum Hydrargyri Oxidi Rubri (Ointment of Red Oxide of Mercury) } 1 part in 8, B.P.; 1 in 10, U.S.P.

With soft and hard paraffin, B.P.; with ointment, U.S.P.

USES.—The red oxide is rarely given internally. The ointment may be used in ophthalmia and conjunctivitis in the same way as the nitrate of mercury ointment, and as an application to the auditory meatus in otorrhœa occurring after scarlet fever. It is also useful in scaly skin-diseases, syphilitic sores on the skin, and in ulcers within the margin of the anus.

Hydrargyrum Ammoniatum, B. and U.S.P. AMMONIATED MERCURY. WHITE PRECIPITATE. NH_2HgCl; 251·1.

CHARACTER.—An opaque white powder.

SOLUBILITY.—It is insoluble in cold water, alcohol, and ether.

REACTIONS.—Digested with caustic potash, it evolves ammonia, acquiring a pale yellow colour, and the fluid, filtered and acidulated with nitric acid, gives a white precipitate with nitrate of silver. Boiled with a solution of chloride of tin it becomes grey, and affords globules of metallic mercury.

PREPARATION.—By dissolving corrosive sublimate in water, and precipitating by ammonia.

IMPURITIES.—Chalk, sulphate of calcium, baryta, lead, carbonates, mercurous salts.

TESTS.—Entirely volatilised at a heat under redness (no chalk, etc.). It should dissolve in hydrochloric acid without residue (no mercurous salt) and without effervescence (no carbonate).

PREPARATION.

B. AND U.S.P.

Unguentum Hydrargyri Ammoniati...1 part in 10, B. and U.S.P. (It was about 15 per cent. B.P. 1867.) With simple ointment, B.P.; with benzoated lard, U.S.P.

USES.—Not used internally. The ointment is used in order to destroy parasitic fungi, but more especially to kill pediculi in the hair or on the body. It is also useful in impetigo contagiosa, lichen, pityriasis, herpes, subacute eczema, and other skin-diseases.

Liquor Hydrargyri Nitratis Acidus, B. and U.S.P. ACID SOLUTION OF NITRATE OF MERCURY. $Hg(NO_3)_2$; 323·7.

CHARACTERS AND REACTIONS.—A colourless and strongly acid solution, which gives a yellow precipitate with solution of potash added in excess (mercuric oxide). If a crystal of sulphate of iron be dropped into it, in a little time the salt of iron, and the liquid in its vicinity, acquire a dark colour (nitrate).

USES.—It is a powerful **caustic**, and is used as such in lupus. It is to be applied with a camel's-hair brush to the extent of a crown piece over the ulcers, tubercles, and scars which are soft and ready to break. The part is then covered with lint moistened in the solution. It soon becomes white, a kind of erysipelatous inflammation sets in around it, and it falls off as a yellow scab. The solution is also applied to the os uteri when there are large ulcers with flabby unhealthy granulations upon it. It has been used in cancer and in chancres, condylomata, syphilitic and scrofulous ulcers, favus, and obstinate psoriasis. If applied often it may cause mercurialism, and indeed salivation has occurred after one application to the os uteri. To prevent this it should be washed off immediately after being applied.

Unguentum Hydrargyri Nitratis, B. and U.S.P. OINTMENT OF NITRATE OF MERCURY. CITRINE OINTMENT.

CHARACTERS.—It has a fine lemon-yellow colour and a consistence like butter. It is apt to become decolourised when mixed with metals or deoxidising powders, and hence an excess of acid is used in order that it may reoxidise them as necessary. It should be spread with a wooden or ivory spatula.

PREPARATION.—By mixing a hot solution of mercury in nitric acid with lard and olive oil, B.P.; or with lard oil, U.S.P.

USES.—This ointment was made in imitation of Singleton's

golden eye-ointment, and it is of remarkable service in ophthalmia tarsi. It should be mixed with its own weight of almond oil and applied to the lids.

It is also applied to phagedænic ulcers and syphilitic sores, and soon destroys the parasitic fungi on which ringworm, &c., depend.

PREPARATION.

B.P.

Unguentum Hydrargyri Nitratis Dilutum (Nitrate of Mercury Ointment 1, Soft Paraffin 2).

U.S.P. Hydrargyri Iodidum Viride. GREEN IODIDE OF MERCURY. Hg_2I_2; 652·6.

CHARACTERS.—A dull green powder, which darkens in colour upon exposure to light.

SOLUBILITY.—It is insoluble in water. When it is shaken in a tube with ether nothing is dissolved.

REACTIONS.—Gradually heated in a test-tube, it yields a yellow sublimate, which, upon friction, or after cooling, becomes red, while globules of metallic mercury are left in the bottom of the tube.

PREPARATION.—By rubbing iodine and mercury together in a porcelain mortar, occasionally moistening with a few drops of spirit.

DOSE.—1 to 3 grains.

USES.—It is employed for the purpose of combining the action of iodine with that of mercury, as in cases of secondary and tertiary syphilis occurring in persons of a scrofulous constitution, and especially in the syphilis of children.

Hydrargyri Iodidum Rubrum, B. and U.S.P. RED IODIDE OF MERCURY. HgI_2; 452·8.

CHARACTERS.—A crystalline powder of vermilion colour, becoming yellow from an alteration in its crystalline form when gently heated over a lamp on a sheet of paper, and again becoming red when placed on a sheet of paper and rubbed with a smooth substance.

SOLUBILITY.—It is almost insoluble in water, dissolves sparingly in alcohol, but freely in ether, or in an aqueous solution of iodide of potassium.

REACTIONS.—When digested with solution of soda it assumes a reddish-brown colour (mercuric oxide); and the fluid, cleared by filtration and mixed with solution of starch, gives a blue precipitate on being acidulated with nitric acid (iodide). Entirely volatilised by a heat under redness.

PREPARATION.—By mixing solutions of corrosive sublimate with potassium iodide in the proper proportions.

DOSE.—$\frac{1}{16}$ to $\frac{1}{4}$ grain.

PREPARATIONS.

B.P.

Unguentum Hydrargyri Iodidi Rubri (Ointment of Red Iodide of Mercury) ... } 1 part in 28.

With yellow wax and almond oil.

B. AND U.S.P.	DOSE.
Liquor Arsenici et Hydrargyri Iodidi	10–30 min.

USES.—It may be used for the same purposes as the green iodide, but, like all the mercuric salts, it is much more powerful than the corresponding mercurous one. It is a powerful local irritant, and is used in the form of ointment in cases of goître. The mode of employing it is to rub the ointment upon the tumour, and afterwards to expose the patient either to the heat of the sun or of a fire as long as he can bear it. This treatment was first used in India. In this country, where the sun's rays are not so powerful, the heat of a fire may be employed, and I have found it efficacious when used in this way. Red iodide ointment is useful in obstinate skin-diseases, especially lupus erythematosus.

It is frequently given in syphilis, one of the most common ways of prescribing it being to give one-half to one drachm of the solution of the perchloride with several grains of potassium iodide. The periodide is thus formed, and is dissolved in excess of the potassium iodide.

U.S.P. Hydrargyri Cyanidum. CYANIDE OF MERCURY. $Hg(CN)_2$; 251·7.

CHARACTERS.—Colourless or white prismatic crystals, becoming dark-coloured on exposure to light; odourless, having a bitter metallic taste, and a neutral reaction.

REACTIONS.—When slowly heated the salt decomposes into metallic mercury and cyanogen gas, which is inflammable, burning with a purplish flame. On further heating, the blackish residue containing globules of metallic mercury is wholly dissipated. On adding hydrochloric acid to the aqueous solution, hydrocyanic acid vapour is evolved.

TESTS.—A 5 per cent. aqueous solution of the salt, when mixed with a dilute aqueous solution of iodide of potassium, should not yield a red or reddish precipitate soluble in excess of either liquid (absence of mercuric chloride).

DOSE.—$\frac{1}{16}$ to $\frac{1}{8}$ grain.

USES.—It may be given in syphilis. A solution of 5–10 grains in an ounce of water, painted on with a camel's-hair brush, is a useful application to syphilitic sores of the tongue or mouth.

U.S.P. Hydrargyri Sulphidum Rubrum. RED SULPHIDE OF MERCURY. HgS; 231·7.

CHARACTERS.—Brilliant dark-red crystalline masses, or a fine bright scarlet powder, permanent in the air, odourless and tasteless.

SOLUBILITY.—It is insoluble in water, alcohol, nitric or hydrochloric acid, or in dilute solutions of alkalis.

REACTIONS.—It is dissolved by nitrohydrochloric acid, and on adding an excess of stannous chloride, metallic mercury is precipitated.

USES.—It is used for mercurial fumigation. Thirty grains may be used instead of calomel, in the way already described (p. 471).

Class IV.

Tetrad Metals.

LEAD. *Titanium.* TIN.

General Actions.—Lead and tin resemble one another to a considerable extent in their physiological action. After absorption into the circulation lead affects the **muscles**, involuntary and voluntary, and the central nervous system. Its action on muscle appears to be first irritant then paralysing. The irritant action on the muscle of the intestine leads to colic, and on the voluntary muscle to cramps in man. In animals, when the quantity administered in experiments at one time is much larger, paralysing action is more marked, and in frogs and rabbits, muscular weakness and rapid loss of irritability both in the voluntary muscles and heart are marked symptoms. In cats the paralysis of voluntary muscle is less marked, and in dogs it is absent.

The **motor area** of the central nervous system appears to be much more affected by lead than the sensory; and in dogs, cats, and pigeons choreic movements and even convulsions occur without impairment of sensation or consciousness. The irritation of the motor centres is succeeded by paralysis and death.

Tin has an action resembling lead in increasing the contractions of the intestinal canal and causing paralysis of the spinal cord. In rabbits it produces weakness and apparent recovery, and then paresis and death.[1]

LEAD. Pb; 207.

General Source of Lead Salts.—Lead is obtained entirely from the native sulphide called galena, by roasting.

General Reactions.—The chief reactions of lead salts are shown in the following table :—

Reagent	Reaction
Hydrogen sulphide . . . } Ammonium sulphide . . }	Black precipitate.
Caustic potash or soda . . .	White „ soluble in excess.
Ammonia	„ „ insoluble „
Carbonates of potassium, sodium, or ammonium . . .	„ „ „ „
Sulphuric acid or sulphates . .	„ „ „ in nitric acid.
Potassium iodide	Yellow „ „

[1] T. P. White, *Archiv f. exp. Path. u. Pharm.* 1880, viii. p. 33.

General Impurities.—Alkaline earths, zinc or copper.

General Tests.—As alkaline earths and zinc are not precipitated by sulphuretted hydrogen, they can be detected by passing this gas through the solution of a lead salt until all the lead has been precipitated as sulphide. On removing the sulphide by filtration, and evaporating the filtrate to dryness, no residue should remain if the lead be pure, U.S.P.

Copper may be detected by precipitating the lead from a solution by sulphuric acid, filtering, and super-saturating with ammonia. If copper be present, the solution will exhibit a blue colour, U.S.P. Insoluble salts, as the oxide, may be dissolved in dilute nitric acid super-saturated with ammonia. The filtrate should show no blue colour.

Action.—Soluble lead-salts unite with **albumen**, and form albuminate of lead. They have little or no irritating action when applied directly to the denuded **skin** or to a mucous membrane. In the mouth they have an astringent action, but a sweet instead of a corrosive taste. In large doses in the **stomach** they may excite vomiting, and may produce symptoms of irritant poisoning. In the **intestine** they act as powerful astringents. After absorption into the blood lead is carried by the blood to all parts of the body, and there becomes deposited. It appears to be eliminated very slowly, so that when even very minute quantities are taken continuously chronic lead-poisoning may be produced.

One of the most important **sources of lead-poisoning** of this sort is drinking water. Soft water attacks the leaden pipes in which it may be conveyed, or the cisterns in which it may be stored, and dissolves enough lead to cause lead-poisoning, the small quantity of one grain per gallon appearing to be sufficient.

Hard waters are not injurious, as they cause a coating of phosphate or sulphate of lead to form on the surface of the pipe or cistern, and thus protect it from further attacks. Other sources of lead-poisoning are beer or cider which has stood in the pipes leading to the tap, and snuff, from the decomposition of the lead-foil which surrounds it. There are certain trades the workers in which are very liable to lead-poisoning, such as colour-grinding, painting, plumbing, type-founding and printing (compositors), or persons making stereotype plates. The chief source of poisoning in these trades is the lead which adheres to the hands and is swallowed along with the food, and the precautions to be adopted are cleanliness, washing the hands carefully before taking meals, taking the food in a different room from that in which the work is carried on, changing the clothes when the work is over, and, if necessary, drinking water acidulated with sulphuric acid.

Treatment of chronic lead-poisoning consists in eliminating the poison, first from the tissues and then from the body. Various means have been employed, such as sulphur baths, the internal administration of sulphur, frequent doses of castor oil. As the lead is eliminated by the skin and mucous membrane, sul-

phur, applied either to the skin or taken internally, will convert it into an insoluble sulphide and prevent its re-absorption. Castor oil will remove from the intestinal canal the lead excreted into it. But the treatment which I employ, and which I find very satisfactory, is to combine the use of iodide of potassium with that of sulphate of magnesium, giving from five to ten grains of the iodide three times a day, and a drachm of the sulphate also three times a day, with an interval of about two hours between the medicines. The object of this treatment is (1) to dissolve the lead deposited in the tissues by means of the iodide (p. 561), and to cause its elimination by the mucus of the alimentary canal, and (2) to render the lead insoluble after it has passed into the intestine by means of the sulphate, and to remove it thence as quickly as possible.

The **symptoms of chronic lead-poisoning** are a blue line on the gums, lead colic, lead cramps, and lead paralysis. The **blue line** on the gums may appear when neither the colic, cramps, nor paralysis are present. It appears to be produced by sulphuretted hydrogen in the mouth precipitating the lead as black sulphide in the gums just at the margin of the teeth, and this, shining through the tissue above it, appears of a bluish colour. It is absent when the teeth have been lost, and slight if they are kept clean.

The **lead colic** may either be preceded by symptoms of digestive derangement, such as loss of appetite, or may appear at once. It is characterised by a tearing pain referred chiefly to the region of the umbilicus, and generally accompanied by obstinate constipation. It is usually, though not always, relieved by pressure, but may sometimes be somewhat increased by it.

Lead cramps are almost entirely confined to the flexor surfaces, specially marked in the calves of the legs, and are usually worse at a change of weather. They may either accompany or succeed the colic.

Lead paralyses are usually confined to the extensor surfaces, and more particularly affect the extensors of the wrist, so that this form of paralysis is sometimes known as **wrist-drop**. The affected muscles become atrophied, and, as the extensor tendons also act as ligaments of the wrist, the bones of the carpus may become displaced. The paralysis probably depends on an affection of the spinal cord rather than of the muscles themselves; for degeneration of the muscles does not occur until after the paralysis has set in for some time, and the muscles are affected in physiological groups which act together, although supplied by different nerves. Thus the supinator longus, which is rather a flexor than a supinator, escapes in lead-poisoning, while the supinator brevis and extensor muscles in the forearm are paralysed In peripheral paralysis of the musculo-spinal

nerve from cold or pressure the supinator longus is paralysed as well as the others.[1]

Cerebral symptoms, consisting of headache, delirium, epileptiform convulsions, or stupor and coma, have been described as occurring in lead poisoning, and have been termed *encephalopathia saturnina*. These have been ascribed to cerebritis caused by the action of lead upon the brain, but it seems not impossible that they are really due to uræmia. If this be so they may be regarded as the direct consequences of the action of lead which, by causing the degeneration of the kidneys to be presently described, leads to imperfect elimination of tissue-waste.

Affections of the eye are sometimes associated with the cerebral symptoms just mentioned, and are noticed in cases where there is no kidney disease. Sudden onset of amblyopia without organic changes may occur, but is then usually transient. The amblyopia consists in a general dimness of vision, or in a diminution of the field of vision of one or both eyes. Optic neuritis (papillitis) also occurs in some cases, and may proceed to atrophy.

Chronic lead-poisoning has a tendency to induce cirrhotic changes in the **kidneys** with albuminuria, the tubules becoming blocked by plugs of lead-carbonate and atrophy ensuing.

Lead appears to cause contraction of the muscular walls of the arteries, and to raise the arterial tension and to slow the heart. This action has been supposed to depend on a local astringent effect upon muscular fibre itself, but as in cases of chronic poisoning the proportion of lead in the nervous system is much greater than in muscular fibre, it is more probable that these effects are of nervous origin. The contraction of the intestine which gives rise to the colic is probably due rather to the action of the lead upon the nerves of the intestine than upon its muscular coats.

Lead is **eliminated**, to a slight extent, in the urine, and probably largely by the mucus of the intestinal canal. It appears to check the elimination of uric acid, and, in London, gout occurs very frequently among patients who work in lead.

Lead-salts may be administered in medicinal doses for a considerable time without bringing on any sign of lead-poisoning; but Garrod has observed, and I can confirm the statement, that the administration of medicinal doses of lead-salts will bring on a fit of gout in persons predisposed to it. Lead-poisoning appears to occur readily in gouty subjects.

USES.—Lead lotions are sometimes applied externally to sprains and bruises. They are useful in relieving the itching and the discomfort of pruritus, and in lessening the discharge of eczema. As injections they may be applied in otorrhœa, vulvitis

[1] Duchenne's Works, selected by Poore, *New Syd. Soc.*

in children, gonorrhœa, and leucorrhœa. They are not used in ulceration of the cornea, lest lead should be deposited in the ulcer and leave a permanent opacity (p. 216). Internally, lead is used for its local action on the stomach in pyrosis, and on the intestine in diarrhœa and dysentery, and for its astringent action on the vessels in hæmatemesis, hæmoptysis, and bleeding from the kidneys and uterus. It has also been employed in palpitation from hypertrophied heart, and in aortic aneurism.

Plumbi Oxidum, B. and U.S.P. Oxide of Lead. PbO; 223.

Character.—In heavy scales of a pale brick-red colour.

Solubility and Reactions.—Completely soluble without effervescence in diluted nitric and acetic acids, either solution, when neutral, giving the reactions of lead (p. 698). It should contain no copper.

Preparation.—By roasting lead in a current of air.

Preparations in which Oxide of Lead is Used.

Emplastrum Plumbi.
„ Saponis Fuscum.
Liquor Plumbi Subacetatis.
Plumbi Acetas.

Emplastrum Plumbi, B. and U.S.P. Lead Plaster.

Preparation.—By heating oxide of lead with olive oil and water. The oleic acid of the oil combines with the lead, forming oleate of lead, and leaving glycerine. This plaster is a lead soap.

Preparations.

B.P.	U.S.P.
Emplastrum Ferri.	Emplastrum Ammoniaci cum Hydrargyro.
„ Galbani.	„ Asafœtidæ.
„ Hydrargyri.	„ Ferri.
„ Resinæ.	„ Galbani.
„ Saponis.	„ Hydrargyri.
	„ Opii.
	„ Resinæ.
	„ Saponis.
	Unguentum Diachylon (1 in 4, nearly).
	And several other plasters into which it enters, as resin plaster.

Uses.—Lead plaster is used to hold together the edges of wounds, to protect irritable surfaces, either alone or by keeping other dressings in contact with them by means of its adhesive power. It is also used as a means of applying pressure.

Unguentum Diachylon (U.S.P.) is very useful in chronic eczema, and in the acute form after severe inflammatory symptoms have subsided. It must be applied thickly spread on a cloth, which is kept in place by a bandage. It is also useful in hyperidrosis, especially of the feet, the treatment being continued, without washing, and with a daily change of dressing, for ten to fourteen days. In sycosis, after shaving, the application of soft soap twice a day, and diachylon ointment in the intervals, has a very beneficial effect.

Plumbi Carbonas, B. and U.S.P. CARBONATE OF LEAD. $(PbCO_3)_2Pb(HO)_2$; 773·5.

CHARACTERS.—A soft, heavy, white powder, blackened by sulphuretted hydrogen.

SOLUBILITY AND REACTIONS.—Insoluble in water, soluble with effervescence in diluted acetic acid without leaving any residue, and forming a solution which gives the reactions of lead.

PREPARATION.—By exposing lead to the fumes of vinegar and to CO_2.

IMPURITY.—Calcium.

TEST.—The acetic solution when treated with excess of sulphuretted hydrogen, boiled and filtered, gives no precipitate with oxalate of ammonium.

PREPARATION.

B. AND U.S.P.

Unguentum Plumbi Carbonatis.........1 part in 8, B.P.; 1 in 10, U.S.P. With simple ointment, B.P.; with benzoated lard, U.S.P.

USES.—Carbonate of lead is used as an application to excoriated surfaces, piles, boils, and ulcers.

The ointment is used in the same way.

Plumbi Acetas, B. and U.S.P. ACETATE OF LEAD. $Pb(CH_2)_2(CO.OH)_2$. $3H_2O$; 378·5. Sugar of Lead.

CHARACTERS.—In white crystalline masses, slightly efflorescent, having an acetous odour, and a sweet, astringent taste.

SOLUBILITY AND REACTIONS.—Its solution in water slightly reddens litmus, and gives the reactions of lead (p. 698) and of an acetate (p. 594).

PREPARATION.—By dissolving oxide of lead in acetic acid.

IMPURITY.—Slight amount of carbonate.

TEST.—Its solution in distilled water is clear, or has only a slight milkiness, which disappears on the addition of acetic acid.

DOSE.—1 to 4 grains.

PREPARATIONS IN WHICH ACETATE OF LEAD IS USED.

B.P.	U.S.P.
Glycerinum Plumbi Subacetatis.	
Liquor „ „ ......5 ounces to 1 pint.	Liquor Plumbi Subacetatis.

Pilula Plumbi cum Opio (*v.* p. 522), 3 parts in 4.
Suppositoria Plumbi Composita...1 part in 5.
Unguentum Plumbi Acetatis.........1 part in 38.

USES.—The acetate is the preparation of lead most frequently used as a local application in inflammations, ulcers, ophthalmia, and gonorrhœa, or for its general actions on the system.

B.P. Pilula Plumbi cum Opio. PILL OF LEAD AND OPIUM.
DOSE.—3 to 5 grains.

USES.—It is a powerful astringent, used either for the purpose of obtaining the local astringent action of lead upon the bowels in diarrhœa, or for its general effect upon the system, after absorption, as in hæmoptysis.

B.P. Suppositoria Plumbi Composita. COMPOUND LEAD SUPPOSITORIES. Each suppository contains 1 grain of opium and 3 grains of acetate of lead.

Uses.—Used in piles and dysentery accompanied by much tenesmus, or in phthisis, where we wish to stop hæmoptysis without putting lead or opium into the stomach and thus running the risk of interfering with digestion.

B.P. Unguentum Plumbi Acetatis. Ointment of Acetate of Lead.—Acetate of lead (12 grains), benzoated lard (1 ounce).

Uses.—It is used as a sedative and astringent application to ulcers, excoriations, painful piles, irritable and itching skin-diseases, erysipelas, burns, bruises, &c.

Liquor Plumbi Subacetatis, B. and U.S.P. Solution of Subacetate of Lead.

Subacetate of lead, $Pb(C_2H_3O_2)_2.PbO$, dissolved in water, B.P. An aqueous liquid containing in solution about 24 per cent. B.P., 25 per cent. U.S.P., of subacetate of lead.

Characters.—A dense clear colourless liquid, with alkaline reaction and sweet astringent taste, becoming turbid by exposure to the air and forming with mucilage of gum-arabic an opaque white jelly.

Reactions.—It gives the reactions of lead and of an acetate.

Preparation.—By boiling acetate of lead, oxide of lead in powder, and distilled water together.

Preparations.

B.P.	U.S.P.
Glycerinum Plumbi Subacetatis.	Ceratum Plumbi Subacetatis.
Liquor „ „ Dilutus.	Linimentum „ „ (v. p. 517).
	Liquor „ „ Dilutus.

Uses.—It is recommended by Ringer as an application to pityriasis and eczema, and in combination with one or two parts of glycerine to the milder forms of lupus after the crusts have been removed. Diluted, and mixed with liquor morphinæ acetatis, it is a useful application to hæmorrhoids.

B.P. Glycerinum Plumbi Subacetatis. Glycerine of Subacetate of Lead.

Preparation.—By boiling acetate of lead, oxide of lead, glycerine and water together and evaporating off the water.

PREPARATION.

B.P. Unguentum Glycerini Plumbi Subacetatis. Glycerine of Subacetate of lead 1, soft paraffin 4, hard paraffin $1\frac{1}{2}$ parts.

Liquor Plumbi Subacetatis Dilutus, B. and U.S.P. Diluted Solution of Subacetate of Lead.—Consists of 2 fl. dr. of solution of lead and 2 fl. dr. of rectified spirit diluted with water up to a pint, B.P. Solution of acetate of lead 3, distilled water 97 parts, U.S.P.

Uses.—Used as a mild astringent and sedative to irritable and itching skin-diseases and superficial inflammation; as an eye-wash unless ulceration of the cornea be present; as an injection in leucorrhœa and pruritus pudendi.

U.S.P. Ceratum Plumbi Subacetatis. Cerate of Subacetate of Lead.—Solution of subacetate of lead (20 parts), camphor cerate (80 parts), U.S.P.

Uses.—Chiefly as an application to chapped hands and ulcers.

U.S.P. Linimentum Plumbi Subacetatis. LINIMENT OF SUBACETATE OF LEAD.—*Vide* p. 517.

USES.—To allay itching in chilblains and skin-diseases.

Plumbi Nitras, B. and U.S.P. NITRATE OF LEAD. $Pb(NO_3)_2$; 330·5.

CHARACTERS.—In colourless octahedral crystals which are nearly opaque, permanent in the air, of a sweetish astringent taste.

SOLUBILITY.—Soluble in water and alcohol.

REACTIONS.—The aqueous solution gives the reactions of lead (p. 698). Added to sulphate of indigo it discharges the colour.

PREPARATION.—By dissolving lead in nitric acid with the aid of heat and crystallising.

PREPARATION IN WHICH NITRATE OF LEAD IS USED.

Plumbi Iodidum.

USES.—It is sometimes applied as a disinfectant, and occasionally to cracked hands or lips and fissured nipples, and in onychia maligna. It has been given in order to check hæmorrhage from the lungs.

Plumbi Iodidum, B. and U.S.P. IODIDE OF LEAD. PbI or PbI_2; 459·7.

CHARACTERS.—A heavy, bright, citron-yellow powder, neutral, with no taste or smell.

SOLUBILITY.—Sparingly soluble in water, readily soluble in chloride of ammonium.

REACTION.—When strongly heated it first fuses and then is decomposed, emitting violet vapours of iodine, and leaving a citron-yellow residue.

PREPARATION.—By mixing solutions of nitrate of lead and potassium iodide.

IMPURITIES.—Chromate, zinc, alkalis, and alkaline earths.

TESTS.—On triturating 1 part of the salt with 2 parts of chloride of ammonium in a porcelain mortar, and adding 2 parts of water, a colourless liquid should result (absence of, and difference from, chromate). This liquid, diluted with water, affords a white precipitate with diluted sulphuric acid, and a black one with hydrosulphuric acid. If all the lead has been precipitated from a portion of the solution by the last-named reagent, the filtrate should leave no residue on evaporation and gentle ignition (absence of zinc, alkalis, or alkaline earths).

PREPARATIONS.

B.P. Emplastrum Plumbi Iodidi. Iodide of Lead Plaster, 1 part in 9 (with soap and resin plaster).

Unguentum Plumbi Iodidi, B. and U.S.P. Ointment of Iodide of Lead; with simple ointment, 1 part in 8, B.P.; with benzoated lard, 1 part in 10, U.S.P.

USES.—It has been used externally as an application to ringworm, and as a counter-irritant in scrofulous enlargement of the glands. It has been given internally in enlarged glands, and in chronic enlargement of the spleen. In the latter case the iodine may be supposed to have a beneficial effect upon the corpuscles of the spleen, and the lead to cause contraction by acting upon the involuntary muscular fibre of the organ.

The ointment is used for enlarged glands.

TIN. Sn; 118.

B.P. Tin, granulated.

Grain tin, reduced to small fragments by fusing and pouring into cold water.

USE.—Used formerly in powder as an anthelmintic in ½ ounce doses.

Solution of Chloride of Tin. $SnCl_2$.

PREPARATION.—By dissolving granulated tin in dilute hydrochloric acid.

USES.—It has a powerful affinity for oxygen and for chlorine. When added to trichloride of gold it gives a precipitate called purple of Cassius whose composition is not known. It is used as a test for mercury. When added to calomel it abstracts chlorine and precipitates metallic mercury. When added to corrosive sublimate it precipitates calomel, which it afterwards reduces to mercury.

Salts of tin are not commonly used in practice, but have been given in nervous diseases in somewhat the same way as zinc.

Chloride of tin is a caustic of considerable power. In poisoning by it the treatment would be to give milk and alkaline carbonates.

CHAPTER XXVII.

METALS—(*continued*).

Class V.—PENTAD ELEMENTS.

NITROGEN, PHOSPHORUS, *Vanadium*, ARSENIC, *Niobium*, ANTIMONY, *Tantalum*, BISMUTH.

In the heading to this class I have substituted the word elements for metals, for nitrogen and phosphorus belong to it, although they are non-metallic elements.

They form analogous compounds with oxygen and hydrogen.

		1	2	3	4	5	
Nitrogen.........	N	... N_2O	... N_2O_2	... N_2O_3	... N_2O_4	... N_2O_5	... NH_3
Phosphorus ...	P			... P_2O_3		P_2O_5	... PH_3
Vanadium	V	... V_2O	... V_2O_2	... V_2O_3	... V_2O_4	... V_2O_5	...
Arsenic	As			... As_2O_3		... As_2O_5	... AsH_3
Antimony	Sb			... Sb_2O_3		... Sb_2O_5	... SbH_3
Bismuth.........	Bi			... Bi_2O_3		... Bi_2O_5	

Nitrogen. N ; 14. Non-officinal.

Nitrogen when free is chemically inactive, and does not readily unite with other elements. It is also physiologically inactive, but has been used as an anæsthetic. The anæsthesia is due to asphyxia, from absence of oxygen ; but as the carbonic acid is constantly removed by the inhalation of nitrogen, the symptoms of irritation produced by it in ordinary asphyxia are absent.

Combined with **hydrogen**, as in ammonia and salts of ammonium, nitrogen stimulates and then paralyses nerve-centres, motor nerves and muscles (p. 144) ; and the action varies in the salts, for while the chloride affects the spinal cord, the iodide paralyses motor nerves and muscles. When nitrogen is combined with **carbon**, the activity of the substance depends on whether the nitrogen is pentad or triad, as in $-N\equiv\equiv C$, and $-C\equiv\equiv N$, in the first of which, with one free affinity belonging to the nitrogen, the compounds are very poisonous, while in the second, where the free affinity belongs to the carbon, the compounds are comparatively harmless.

The 1st, 3rd, and 5th of its **oxygen** compounds in the above table can take up the elements of water and of metallic oxides to form salts.

Hydrogen Salt.		Metallic Salt, e.g. of Potassium.	
Hyponitrous acid	H_2ON_2O or HNO.	Potassium hyponitrite	K_2ON_2O or KNO.
Nitrous acid	$H_2ON_2O_3$ or HNO_2.	" nitrite	$K_2ON_2O_3$ or KNO_2.
Nitric acid	$H_2ON_2O_5$ or HNO_3.	" nitrate	$K_2ON_2O_5$ or KNO_3.

The acid compounds of nitrogen with oxygen resemble those of phosphorus and arsenic in this, that the nitrites are considerably more active than the nitrates, just as the phosphites and arsenites are more active than the phosphates and arseniates. The action of nitrites on the organism was first investigated in the case of nitrite of amyl, but by some unpublished experiments made in Professor Ludwig's laboratory in 1869–70, I satisfied myself of the correctness of Dr. B. W. Richardson's observation,[1] that other nitrites, such as those of ethyl and sodium, had an action on the blood-pressure similar in kind though less in degree. In other experiments Dr. Gresswell and I found that the nitrites of propyl and butyl had also this action, and that all nitrites were muscular poisons.[2] Mr. Tait and I found that nitroglycerine had an action resembling the nitrites both in its effect on blood-pressure and the change it caused in the colour of the blood, but the headache it produced deterred us from employing it in the treatment of patients.[3]

Nitrous Oxide. Nitrogen Monoxide. Laughing gas. N_2O. Not officinal.

Preparation.—By heating nitrate of ammonium.

Action.—When a mixture of nitrous oxide and air is inhaled it causes excitement, generally characterised by fits of involuntary laughter, dancing, singing, and shouting, although it sometimes appears to arouse pugnacity. When inhaled pure, it produces, first of all, a feeling of increased circulation through the body generally, accompanied by warmth and a little singing in the ears. If the inhalation be now stopped, the effect may pass off, but occasionally, after a few breaths of pure air have been taken, the same excitement may ensue which is usually produced by the inhalation of mixed air and gas. On one occasion, having inhaled pure gas for a short time, I felt a little warmth of the skin and a humming in the head, and, thinking it was time to desist, laid down the mask of the inhaler. After a few breaths of fresh air, I noticed that on attempting to speak, the speech was slow and hesitating. An electric shock then seemed to shoot through the spine, and I was seized with an uncontrollable desire to laugh, jump, and throw the arms about, while the perceptive faculties appeared quite unaffected. Although unable to control my movements, I was perfectly conscious of their ludicrous nature, and was astonished that two men who were sitting by, and who afterwards informed me that they thought the whole

[1] B. W. Richardson, *Brit. and For. Med. Chir. Rev.*, July, 1867.
[2] *St. Bartholomew's Hospital Reports*, 1876, p. 143. [3] *Ibid.* p. 140.

thing a bad joke, were able to preserve their gravity. After lasting for one or two minutes, the effect of the gas suddenly and completely passed off.

When inhalation is continued for a longer time, the feelings of warmth and buzzing in the ears are succeeded by gradually increasing dimness of perception; sight, sounds, and tactile impressions become much dimmer than usual: and then the person becomes unconscious. At this time the face usually assumes a livid aspect, and during the period of insensibility small operations may be performed without the patient being the least aware of them. When the administration of the gas is stopped, recovery quickly and completely occurs, often passing off without leaving any after-effects, though occasionally more or less headache is experienced for some hours. No stage of exhilaration such as that which has already been described as occurring after the administration of a small quantity of nitrous oxide is noticed during recovery from complete narcosis.

Nitrous oxide appears to act as an anæsthetic chiefly by depriving the nerve-centres of oxygen. As the inhalation of pure nitrogen has a similar anæsthetic power, the exhilarating effect of small doses of nitrous oxide seems to show besides that it has a special relation to the nerve-centres.

USES.—It is useful as an anæsthetic for extraction of teeth, evulsion of the toe-nail, and other minor operations. The intense venosity of the blood which occurs during its use renders it unsuitable for continued administration, and therefore inadmissible in the case of lengthy operations. It is sometimes used to commence anæsthesia, ether being given after the patient is unconscious.

MODE OF ADMINISTRATION.—The most convenient mode of administering it is to have it condensed in a large iron bottle, from which the gas may be readily conveyed to the patient by means of a flexible tube attached to a mask. The mask ought to be provided with a margin of inflated india-rubber, so that it will fit perfectly tight to the face, and thus prevent the escape of gas. After the operation it is well to make the patient perform some act, such as taking hold of the glass of water after a tooth has been extracted, in order to hasten the return of consciousness.

PHOSPHORUS. P; 31. B. and U.S.P.

A non-metallic element obtained from bones.

CHARACTERS.—A semi-transparent, yellowish, waxy-looking solid. When exposed to air it emits white fumes which are luminous in the dark and have a garlicky odour.

PREPARATION.—By treating bones with sulphuric acid, when sulphate of calcium is precipitated and acid phosphate of calcium remains in solution.

This is evaporated and distilled with charcoal, which removes the oxygen. The phosphorus distils over and is condensed under water.

OFFICINAL PREPARATIONS.

B.P.	DOSE.
Pilula Phosphori ($\frac{1}{50}$ gr. in 3 grs.) (p. 522)	2–4 grs.
Oleum Phosphoratum (phosphorus in almond oil, about 1 per cent.) ...	1–10 m.

U.S.P.	
Pilulæ Phosphori ($\frac{1}{100}$ gr. in each) (p. 523)	1–5 pills.
Oleum Phosphoratum (with stronger ether and almond oil 1 per cent.) ...	1–5 m.

ACTION OF PHOSPHORUS.—Living protoplasm has the power of oxidising all the members of this group, and also of reducing the products of their oxidation (Binz). It is probable that this action goes on more easily with phosphorus than with nitrogen. Hence if phosphorus replaces nitrogen in a living cell it will quicken metabolism. It is absorbed unchanged into the blood, and is excreted by the kidneys either as phosphorus or phosphoric acid. In small doses it appears to cause development of the fibrous tissue in the liver, and in doses too small to affect the liver or stomach it acts upon the osseous tissues. Its action upon the bones is somewhat peculiar, and has been fully investigated by Wegner. When phosphorus is given to growing animals the bone as it develops is denser than usual, the cancellous tissue being like the denser tissue in the long bones. Cancellous tissue formed before the administration of phosphorus remains unchanged. If the administration be still continued, the cancellous tissue formed previously to the use of the drug is absorbed, and serves to form the cavity of the bone, and after a while the normal cancellated tissue at the end of the epiphysis is also replaced by solid bone. Afterwards even the dense bone thus formed becomes absorbed, and forms the cavity of the long bone. In adult animals phosphorus also causes the bones to become denser, and this is especially noticeable in chickens, in which the cavity of the bone may be completely filled up, so that long bones form a solid rod instead of a tube. The influence of phosphorus upon osseous tissues is not due to excess of phosphates produced by it in the blood, but to stimulation of tissue-growth itself by the phosphorus, for Wegner found that in animals fed with phosphorus but almost entirely deprived of phosphates, the same dense, bony substance was formed, except that instead of the bone being hard, it was like that which occurs in rickets. In men and women exposed to the fumes of phosphorus, e.g. those employed in the manufacture of lucifer-matches, caries of the lower jaw is a frequent occurrence. This is not due to the action of the phosphorus after absorption into the circulation, but to the direct effect of the fumes upon the bone itself. For it has been found that when a bone of an animal fed by phosphorus was exposed, no carious change took place; but if one were exposed to the fumes, caries was produced, and amongst

lucifer-match makers it has been noticed that only those who have carious teeth suffer from necrosis of the jaw. When doses larger than those which induce induration of the bones are given, the phosphorus appears to act upon the **connective tissue** of the **stomach** and **liver**, causing chronic inflammation of these organs, and atrophy of the secreting cells, so that cirrhosis of the liver appears. In **poisonous doses** phosphorus first produces the symptoms of gastro-enteritis, with a garlicky taste in the mouth, the vomited matters having a similar odour, containing bile, and, but rarely, blood. They sometimes shine in the dark. At the end of twenty-four to thirty-six hours, the symptoms of gastro-intestinal irritation cease, and the patient is apparently well with the exception of vague pains in the limbs and loins. During this period, however, fatty degeneration of the liver, stomach, and **kidneys** is going on, and the effect of the changes in these organs soon manifests itself. Sometimes, after two or three days, the patient may die suddenly, without exhibiting any fresh symptoms, but usually, on the second or third day, jaundice appears, while the urine contains bile, and often albumen, leucin, and tyrosin. There is occasionally vomiting and purging, headache, sleeplessness, delirium, and coma, and death with or without convulsions. In some cases, when the poisoning runs a less acute course, the effect of fatty degeneration of the **vessels** is most prominent, discharges of blood occurring from the stomach, intestines, nose, lungs, bladder, uterus, and ears, and ecchymoses appearing on the surface. Increasing anæmia and debility finally kill the patient.

The **treatment** in cases of poisoning by phosphorus is to wash out the stomach freely by means of the stomach-pump,' or to employ it by an emetic of sulphate of copper, and to give oxidised oil of turpentine in 40-minim doses in mucilage every fifteen minutes for an hour. Fats and oils should be withheld, as they dissolve any phosphorus which may be present in the stomach, and assist its absorption.

The **fatty degeneration** produced by phosphorus appears to depend on a more rapid splitting up of albuminous tissues, along with deficient oxidation. This was shown by Voit and Bauer, who produced fatty degeneration of the organs by the administration of phosphorus in dogs absolutely deprived of food, where the fat found after death could neither have come from food nor from fat deposited in other parts of the body, as this had all been absorbed before the administration of the drug had been commenced. It must therefore have been formed *in situ* from the decomposition of albuminous substances, and these were shown to have split up more quickly than usual by the amount of urea in the urine being increased by the phosphorus, while oxidation in the body was shown to have diminished by the amount of oxygen absorbed and carbonic acid given off being lessened. In

man, the products of albuminous waste are often not converted into urea, but appear in the urine as leucin and tyrosin.

The action of **compounds** containing phosphorus appears to depend considerably on the more or less complete saturation of its affinities, and the readiness with which the phosphorus may attach itself to the organic constituents of the tissues. Thus, phosphoric acid, in which the affinities of the phosphorus are fully saturated by oxygen, appears simply to act as an acid without exerting any specific action, and when combined with sodium, its effects are simply those of a neutral alkaline salt.

Metaphosphoric and pyrophosphoric acids appear to have a specific poisonous action more nearly resembling that of phosphorus. Pyrophosphate of sodium paralyses the nerve-centres in the spinal cord and medulla oblongata, producing drowsiness, loss of reflex action, paralysis, and death, which is sometimes preceded by convulsions. It lowers the blood-pressure in mammals, slows the beats of the frog's heart, renders them powerful and finally arrests them in systole. When death does not occur rapidly, marked fatty degeneration of the heart and kidneys is found, and a similar change takes place, though to a less extent, in the liver. Although it acts as a poison when injected subcutaneously or into the circulation, pyrophosphate of sodium has no poisonous action when taken into the intestinal canal.

Metaphosphate of sodium has a similar but less powerful action.

Uses.—Phosphorus forms an important constituent of nervous tissue, and has been employed in cases of nervous debility, neuralgia, wakefulness, paralysis, locomotor ataxia, and impotence. In some cases of leucocythæmia it is useful. It has been used in osteomalacia, and instead of arsenic in skin-diseases (*vide* also p. 719). Even in small doses it may cause nausea, with unpleasant eructations. It is well, therefore, to commence with a very small dose, such as $\frac{1}{100}$ of a grain.

ARSENIUM (ARSENIC). As; 75.

Metallic arsenic is not used in medicine. It is steel-coloured, crystalline, and brittle, and when heated gives off garlicky fumes. Very light (sp. gr. 5·8), very volatile. It forms two classes of salts. In one—the arsenious salts—it is tri-, in the other—arsenic salts—pent-atomic. Arsenious oxide, As_2O_3, usually called arsenious acid, forms arsenites. Arsenic oxide, As_2O_5, or arsenic acid, forms arsenates, or, as they are termed in the B. and U.S.P., arseniates.

General Sources of Arsenic.—It occurs in many ores combined with metals, oxygen, and sulphur. Its presence as a frequent impurity in sulphur

has already been mentioned (p. 543). It is chiefly obtained by roasting the arsenides of iron, nickel, and cobalt, and condensing the arsenious oxide in a long, nearly horizontal, chimney.

General Tests for Arsenious Acid.—With hydrosulphuric acid it gives a yellow precipitate, which is brightest in acid solutions. Silver nitrate gives a canary-yellow and copper sulphate a brilliant green precipitate (Scheele's green). These are very soluble in acid, and neither of them is thrown down from simple aqueous solutions of arsenious acid (a little acid being freed in the reaction); a little alkali must be present. Both are very soluble in excess of ammonia, so that to avoid adding excess ammonio-nitrate of silver and ammonio-sulphate of copper are used as reagents, in preference to adding ammonia, along with simple solutions of nitrate of silver or of sulphate of copper. Arseniates throw down a brick-red precipitate with ammonio-nitrate of silver, and are thus distinguished from arsenites.

General Reactions of Arsenic, Antimony, and Bismuth.

	Arsenic	Antimony	Bismuth
Hydrosulphuric acid	Yellow precipitate (soluble in ammonium sulphide and re-precipitated by acids).	Orange or brick-red precipitate (soluble in ammonium sulphide, and precipitated by acids).	Black precipitate (insoluble in ammonium sulphide).
Water . . .	. . . . . .	Strong solution thrown into much water gives a white precipitate, which becomes orange on the addition of hydrosulphuric acid.	Strong solution thrown into water gives a white precipitate, which becomes black on the addition of hydrogen sulphide.

General Action of Arsenic.—Although arsenic, like antimony, has no great affinity for albumen, and does not produce with it a coagulum, yet when applied to the **skin** denuded of its epidermis, it acts as a caustic and produces a slough. If used in a dilute form, and over a large surface, it may be absorbed, and may produce the general effects of the drug upon the system. When applied in a concentrated form it appears to produce a slough more rapidly, and the dead tissue forms a barrier to its further absorption. In the **mouth** it has a somewhat sweetish taste, and in small doses excites in the **stomach** a feeling of appetite. In larger doses it produces irritation, colicky pains, diarrhœa, and mucous evacuations, sometimes tinged with blood. In still larger doses it causes symptoms of gastro-enteritis, vomiting, and purging, the stools being finally of a rice-watery appearance, closely resembling those of Asiatic cholera. These are also occasionally accompanied by collapse, with pale, pinched, and somewhat livid surface, and violent cramps of the extremities, so that cases of arsenical poisoning may be readily mistaken for cholera, and *vice versâ*. There is sometimes strangury, priapism, suppression of urine or bloody urine; the consciousness is retained to the last. In some cases there are no symptoms at all of gastro-intestinal irritation, the **nervous system** being

affected, and the patient presents the symptoms of coma, very much resembling those of opium-poisoning.

The **treatment** in cases of arsenical poisoning is to wash out the stomach freely by means of the stomach-pump, and the copious administration of diluents, taking care to ensure their evacuation by the subsequent speedy administration of such emetics as mustard or sulphate of zinc if they are not at once rejected by the vomiting caused by the arsenic itself. Freshly-prepared peroxide of iron may be administered in doses of a tablespoonful every ten minutes, and alcohol has been given when the moist peroxide could not be obtained. Demulcents should afterwards be given to allay the irritation.

Chronic poisoning by arsenic may occur from the inhalation of arsenical vapour or dust, arising from wall-papers, dresses, or other substances containing arsenic. The proportion of arsenic necessary to produce poisoning when taken into the lungs in this way appears to be very small. The symptoms are at first increased appetite, then colicky pains and mucous or dysenteric stools, with great prostration, irritation of the eyes, running at the nose, a short cough, which is dry or accompanied by slight expectoration, and a white silvery appearance of the tongue. These symptoms may sometimes continue for months, or even years, without the cause being suspected, until the recovery which ensues upon the removal of the offending wall-paper gives the clue to their cause.

When taken internally for a length of time a condition of **tolerance** may be induced in the case of arsenic, as well as in that of antimony. This is seen in the arsenic-eaters of Styria, who, beginning with small quantities, are gradually capable of taking larger and larger doses, until they can swallow at once, with safety, as much as five grains. In taking such doses as these they are careful not to take water with the arsenic, so that it is probably slowly absorbed from the stomach, and is, very possibly, rapidly evacuated. Dr. Craig Maclagan watched a noted arsenic-eater swallow his dose, and obtained from the urine which he afterwards passed a considerable quantity of the poison. By using the arsenic in this way, these people are said to undergo much greater exertion than usual without exhaustion, and to be able to ascend the steep Styrian hills without being affected with breathlessness. Some, no doubt, die in the attempt to acquire the habit, but those who have once become accustomed to the drug appear to continue its use without deriving any harm from it, and, moreover, seem sturdy and vigorous, and live to an old age.

After absorption into the blood, arsenic appears to some extent to modify **tissue-change**. When a solution of arsenious acid is added to **blood** outside the body, it retards coagulation, prevents putrefaction, and conserves the form of the red blood-corpuscles.

A very dilute arsenical solution also conserves the irritability of the excised nerve and muscle of the frog.

Considerable doses of arsenic given for a length of time produce fatty degeneration of the liver and other organs, and cause the **glycogen** to disappear from the liver, so that puncture of the fourth ventricle no longer produces glycosuria.

Minute doses of arsenic appear to increase the rapidity of the **pulse**. Larger doses diminish the pulse and blood-pressure. In frogs the heart is slowed, and finally stands still in diastole. This stoppage of the **heart** appears to be due to paralysis of the motor ganglia, as the muscular substance will still continue to contract upon direct irritation. In warm-blooded animals it appears to prolong the irritability of the heart, so that it will still continue to beat for many hours after the death of the animal. According to Küntzer, this is due to retardation of the vital processes in the mammalian heart, so that it comes to resemble that of a cold-blooded animal. In animals, arsenic has been found to diminish the **blood-pressure** from the beginning. This appears to be due partly to diminished activity of the heart, but chiefly to paralysis of the splanchnics allowing the abdominal vessels to dilate (p. 284). In frogs it produces apparent paralysis, but this appears

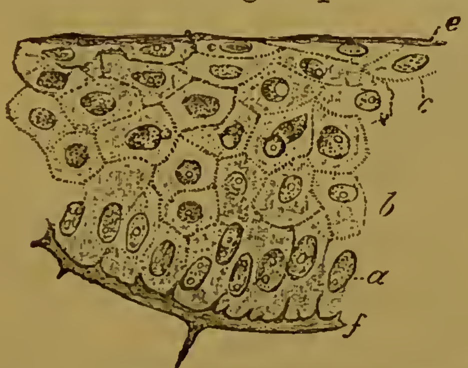

FIG. 169.—Vertical section of the healthy epidermis of a frog. *a*, Columnar layer of cells. *b*, Malpighian layer. *c*, Intermediate layer. *e*, Corneous layer. *f*, Sheet of connective tissue forming boundary between dermis and epidermis. (After Nunn.)

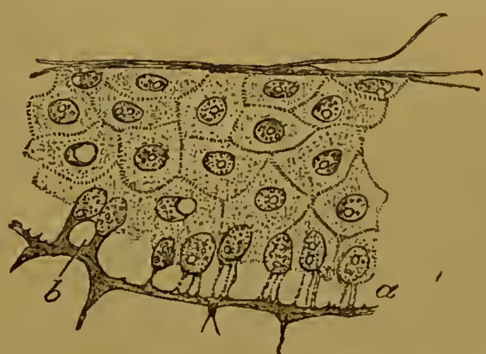

FIG. 170.—Vertical section of epidermis from a frog poisoned by arsenic. *b*, vacuole in the softened protoplasm of the columnar layer of cells. At *a* the protoplasm is more softened and the vacuoles enlarged so that the cells are attached to the dermis only by threads of protoplasm. (After Nunn.)

rather due to diminished sensibility of the grey matter in the posterior cornua of the spinal cord than to real paralysis; for the nerves and muscles in this state are found to be still quite irritable, and although the animal is insensible to pinching it can and does move when laid on its back. As, according to Schiff, the muscular sensations are conveyed in the white substance of the posterior columns, this would appear to be unaffected, while the grey substance which conveys sensations of pain is completely paralysed (p. 160).

In some cases of poisoning by arsenic, **paralysis** of one or more limbs occurs after the acute symptoms have passed off. It usually affects the extensors more than the flexors, and is generally temporary, though it may be permanent.

The action of arsenic on the **skin** is peculiar. Ringer and Murrell noticed that in frogs poisoned by it the cuticle could be stripped off the whole body with the greatest readiness within a few hours after its administration. This condition was found by Nunn to depend upon softening of the protoplasm of the columnar layer of cells in the epidermis, so that the cuticle remained attached to the dermis only by a few protoplasmic threads (Figs. 169 and 170).

Other epithelial structures are also affected, and Cornil has found fatty degeneration of the epithelium lining the alveoli of the **lungs** in animals poisoned by arsenic (Fig. 171).

Arsenic is **eliminated** chiefly by the urine, and to a less extent by the bile, and slightly by the skin. Its elimination by the urine is very rapid.

USES.—Arsenic has been used externally as a **caustic** application to cancers, and forms the basis of most of the secret 'cures'

FIG. 171.—Section of lung, hardened in osmic acid, from guinea-pig poisoned by arsenious acid. The capillaries, *v*, project into the cavities of the alveoli, and are full of red blood-corpuscles. The protoplasm, *a*, of the cells is filled with fatty granules. The nuclei are well preserved. (After Cornil.)

for this disease. The old recipe for this purpose consists of the following ingredients: Arsenious acid, 2 drachms; cinnabar, 2 drachms; ashes of old leather, 8 grains; dragon's blood, 12 grains, made into a paste with water or saliva.

In applying a paste of this sort it is advisable that it should consist of at least one-fifth of arsenic, and that it should not be applied to too large an extent of surface at a time. The arsenical paste used by Hebra consisted of arsenious acid 1 gramme, cinnabar 3 grains, and emollient ointment 24 grains.

Internally, arsenic is used for its local action on the intestinal canal as a **tonic** and **astringent**, for its action on tissue-change, and as a tonic and **anti-spasmodic** in cases of nervous disease. In the stomach, small doses stimulate the appetite, and are useful in allaying pain and checking vomiting. It may be given in irritative dyspepsia, in gastralgia, heartburn, in the vomiting of drunkards, and in gastric ulcer or cancer. It is also recommended by Ringer in cases of regurgitation of food unaccompanied by nausea. It is very useful in cases of diarrhœa where the ten-

dency comes on during or immediately after the ingestion of food, whether in adults or children; it is then best given in small doses before meals (p. 387).

Arsenic is a powerful **antiperiodic**, nearly rivalling quinine; it seems less serviceable than quinine in well-marked cases of ague, but is sometimes as good, or even better, than it in the irregular malarious manifestations such as headache, neuralgia, &c., which are known under the head of masked malaria. It is sometimes useful in chronic rheumatism and rheumatic gout, and in neuralgia of various sorts its effects are occasionally almost magical.

It has been used, not only in tic and hemicrania, but in spasmodic nervous diseases such as angina pectoris, chorea, and epilepsy, whooping-cough and asthma. It is often very serviceable in hay fever, and in cases of spasmodic sneezing coming on after exposure to dust or even without any apparent cause. It has been employed in chronic bronchitis with copious expectoration, and in ordinary catarrh without febrile disturbance. It appears to be very useful in the commencement of phthisis. Under its influence the author has seen consolidation of the lung, consequent on catarrhal pneumonia, clear up completely, even in a subject having a very bad family history.

Probable mode of action of Arsenic in Phthisis.

The treatment of phthisis is so important that it may be advisable to discuss in a few words the probable mode of action of arsenic and hypophosphites in its early stages. It is now probable that this disease depends on the presence of a **bacillus** (*B. tuberculosis*, p. 83). In order that it should grow within the body, however, it is necessary that a suitable **nidus** should be present, and the different susceptibility to the disease of different individuals, or of the same individual at different times, probably depends on their liability to present a suitable nidus. The *Bacillus tuberculosis* differs from such bacilli as the *B. anthracis* in being of a very slow growth, so that when it is cultivated artificially on a solid medium it takes about ten days before it succeeds in establishing itself and begins to grow. Consequently, when applied to an open wound, or when inhaled into the lungs of a healthy person, it does not, like the *Bacillus anthracis*, at once begin to multiply and produce disease in the organism, but it is usually removed by washing in the case of a wound, or by expectoration in healthy persons. But if its removal be interfered with it will produce disease. Thus, if instead of being applied to an open wound it be injected under the skin so that it cannot be removed by washing, it will after a time begin to grow, and produce tuberculosis, first local and then general. It is probable that the case is similar in the lungs. In the healthy lung it finds no nidus, and is removed by expectoration, but if a

portion of the lung be consolidated by catarrhal pneumonia, the consolidated part probably affords a nidus to the bacillus, and the longer the consolidation lasts the greater the risk of bacilli finding entrance. In croupous pneumonia the exudation into the alveoli, consisting chiefly of fibrin with a few leucocytes, quickly breaks up and is absorbed, so that it is comparatively rarely followed by phthisis. But the proliferated epithelial cells which fill the alveoli of the lung in catarrhal pneumonia are much more resistant; they break down and are absorbed much more slowly, and hence a much longer time is given during which bacilli may find a nidus. The marked hereditary nature of phthisis is a curious point in a disease which we suppose to depend on the presence of a bacillus, and is a character in which it differs from such diseases as anthrax, ague, or relapsing fever, which are also due to foreign organisms. But the difference probably depends on the slow growth of the tubercle bacillus, which renders a prolonged undisturbed rest at the point where it enters the body necessary for its further growth. The disease is not hereditary, but the predisposition to such morbid changes in the lungs as affords a nidus to the bacilli is hereditary.

The more rapidly the effused products in pneumonia can be removed from the lung, the less chance have the bacilli of finding a nidus. It is probable that arsenic, which causes fatty degeneration of the normal epithelial cells lining the alveoli, also causes a similar degeneration of such cells when filling the alveolar cavities. By thus breaking them up and quickening their absorption, arsenic will lessen the risk of bacilli finding a nidus in them and converting catarrhal consolidation into phthisis. Probably the hypophosphites act in a similar way. If the patient should be in places where there are no tubercle bacilli, the consolidation may persist for a long time without phthisis occurring, and hence one advantage of sea-voyages in cases of recent consolidation.

Mode of Administration.—In those cases where the local action of arsenic on the stomach and intestine is desired, it is best to give it in small doses before meals, but where the action of the drug on other organs of the body is desired, it should be administered immediately after meals.

The symptoms which show that arsenic is beginning to produce its physiological effect, and that it is time to diminish the dose or cease its administration, are irritation of the eyes, with a pricking sensation in them, the conjunctivæ being somewhat injected, and the patient showing a tendency to rub the eyes; or the digestive canal may be the first to show the effect of the drug, the tongue being covered with a thin white silvery fur, or red, with enlarged fungiform papillæ; the appetite may fail, and colicky pains with a tendency to diarrhœa may appear before the

eyes are affected. Either of these symptoms indicates that the drug should be discontinued, or the dose diminished.

In skin diseases arsenic is used more frequently than any other internal remedy. As it increases metabolism in the cells of the epidermis (p. 716) it is contraindicated in acute cases, or when there is any active cutaneous inflammation in a chronic case. It is sometimes useful in chronic eczema when associated with chlorosis, and in lupus, chronic urticaria, and the neuralgia following herpes zoster. According to Mr. Hutchinson it cures pemphigus. The skin-diseases, however, in which arsenic is most useful are psoriasis and lichen ruber; beginning with two minims of Fowler's solution three times daily, the dose should be gradually increased to 12 minims or even 30 minims daily, and it should be given until either the amendment begins, or the signs of conjunctivitis or gastric irritation appear. When these are noticed, the dose should be diminished until they become just perceptible, and the administration of the drug should be continued for some time after the eruption has disappeared, in order to prevent its recurrence.

Acidum Arseniosum, B. and U.S.P. ARSENIOUS ACID. As_2O_3; 197·8.

An anhydride (not a true acid), obtained by roasting arsenical ores, and purified by sublimation.

CHARACTERS.—Occurs in sublimed masses which usually present a stratified appearance caused by the existence of separate layers differing from each other in degrees of opacity, or as a heavy white powder. When slowly sublimed in a glass tube it forms minute brilliant and transparent octahedral crystals.

SOLUBILITY.—It is sparingly soluble in water.

REACTIONS.—Its solution gives with ammonio-nitrate of silver a canary-yellow precipitate insoluble in water, but readily dissolved by ammonia and by nitric acid. Sprinkled on a red-hot coal it emits a garlicky odour.

IMPURITIES.—Gypsum and chalk.

TEST.—It is entirely volatilised at a temperature not exceeding 400° F. Four grains of it dissolved in boiling water with eight grains of bicarbonate of sodium discharge the colour of 808 grain-measures of the volumetric solution of iodine. $As_2O_3 + 2H_2O + 4I = As_2O_5 + 4HI$.

DOSE.—$\frac{1}{60}$ to $\frac{1}{12}$ of a grain, in solution. It may also be given in the so-called 'Asiatic pills,' which are used in some parts of the Continent. These consist of arsenious acid, 0·75 grm., powdered black pepper, 6 grm., gum arabic, 1·5 grm., powdered marsh-mallow root, 2 grammes, to make 100 pills, of which three are to be taken daily.

PREPARATIONS OF ARSENIOUS ACID.

B.P.	DOSE.
Liquor Arsenicalis	2–8 min.
,, Arsenici Hydrochloricus	2–8 min.
U.S.P.	
Liquor Potassii Arsenitis	2–8 min.
Liquor Acidi Arseniosi	5 min.

PREPARATIONS OF ARSENIC ACID.

B. AND U.S.P.

Ferri Arsenias. Sodii Arsenias. Liquor Sodii Arseniatis.

Liquor Arsenicalis, B.P.; Liquor Potassii Arsenitis, U.S.P. ARSENICAL SOLUTION, B.P.; SOLUTION OF ARSENITE OF POTASSIUM, U.S.P. FOWLER'S SOLUTION.—Is a mixed solution of arsenite and carbonate of potassium flavoured with compound tincture of lavender. Contains 1 part arsenious acid in 100 of water, or about 4½ grains in 1 fl. oz., B. and U.S.P. In the B.P. 1867, it contained 4 grs. in 1 fl. oz., or 1 in 109.

CHARACTERS.—A reddish liquid, alkaline to test-paper, and having the odour of lavender.

REACTION.—After being acidulated with hydrochloric acid, it gives, with sulphuretted hydrogen, a yellow precipitate, which is brightest when the arsenical solution has been previously diluted.

DOSE.—2 to 8 minims.

USE.—This is the preparation of arsenic most commonly employed. It may be given along with alkalis.

Liquor Arsenici Hydrochloricus, B.P.; Liquor Acidi Arseniosi, U.S.P. HYDROCHLORIC SOLUTION OF ARSENIC, B.P.; SOLUTION OF ARSENIOUS ACID, U.S.P.—A solution of arsenious acid, 87 grs. with 2 fl. dr. of hydrochloric acid in 20 fl. oz. of water, B.P.; 1 part arsenious acid and 2 of hydrochloric in 100 of water, U.S.P. It is a 1 per cent. solution in both Pharmacopœias.

CHARACTERS AND REACTION.—A colourless liquid, having an acid reaction. Sulphuretted hydrogen gives at once a bright yellow precipitate.

DOSE.—2 to 8 minims.

USE.—Some think it milder than the ordinary liquor. Garrod thinks not. It can be given along with perchloride of iron in solution, or with acids.

Sodii Arsenias, B. and U.S.P. ARSENIATE OF SODIUM. $Na_2HAsO_4.7H_2O$; 311·9.

CHARACTERS.—In colourless transparent prisms.

PREPARATION.—By fusing arsenious acid with nitrate and carbonate of sodium. The As_2O_3 is oxidised by the nitrate to As_2O_5, which combines with the sodium to form arseniate.

SOLUBILITY.—It is soluble in water.

REACTIONS.—The solution in water is alkaline, giving white precipitates with chloride of barium, chloride of calcium, and sulphate of zinc, and a brick-red precipitate with nitrate of silver (arseniate), all of which are soluble in nitric acid.

DOSE.—$\frac{1}{16}$ to $\frac{1}{8}$ gr.; of the dried salt, $\frac{1}{24}$ to $\frac{1}{12}$ gr.

PREPARATIONS.

B. and U.S.P.

Liquor Sodii Arseniatis. 4½ grains dried in 1 fl. oz. of water, or 1 in 100, B. and U.S.P.

DOSE.—5 to 10 minims.

ACTION.—It acts like other preparations of arsenic, but does not irritate the stomach so much, and may be given in larger doses. In frogs it produces, like arsenious acid, paralysis of the

brain and spinal cord, but is much less powerful (Ringer and Murrell).

USES.—It may be used in the same diseases as arsenious acid. It is perhaps one of the best remedies for neuralgia which we have.

Arsenii Iodidum, B. and U.S.P. IODIDE OF ARSENIUM, B.P.; OF ARSENIC, U.S.P. AsI_3; 454·7.

CHARACTERS.—Small orange-coloured crystals.

SOLUBILITY.—Readily and almost entirely soluble in water and in rectified spirit.

REACTIONS.—Its aqueous solution has a neutral reaction, and gives a yellow precipitate with sulphuretted hydrogen. Heated in a test-tube it almost entirely volatilises, violet vapours of iodine being set free.

PREPARATION.—By the direct combination of iodine and metallic arsenic, or by evaporating to dryness an aqueous mixture of arsenious and hydriodic acids.

DOSE.—$\frac{1}{30}$ gr.

USE.—In skin diseases.

Liquor Arsenii et Hydrargyri Iodidi, B. and U.S.P. SOLUTION OF IODIDE OF ARSENIC AND MERCURY. DONOVAN'S SOLUTION.[1] Iodide of arsenium, AsI_3, and red iodide of mercury, HgI_2, of each 45 grains (1 per cent. of each by weight), water up to 10 fl. oz., B.P. Iodide of arsenic, 1; red iodide of mercury, 1; water up to 100, U.S.P.

CHARACTERS.—A pale yellow liquid, with a metallic taste.

INCOMPATIBLES.—Solutions of opium or morphine.

DOSE.—5 to 30 minims (0·3–1·8 c.c.).

USES.—In skin diseases, syphilis, rheumatism, and nocturnal pains.

ANTIMONY. Sb; 122.

Antimony forms two classes of salts, antimonious and antimonic. In the former it is tri- and in the latter pent-atomic.

GENERAL SOURCES.—It is chiefly found native in the form of the black antimonious sulphide, Sb_2S_3.

GENERAL REACTIONS.—It is recognised by the orange-coloured precipitate which it gives with sulphuretted hydrogen in acid solutions. A characteristic reaction is the white precipitate which falls on throwing a strong solution of a salt of antimony, such as the chloride, into water, and the change of the white into an orange colour on the addition of sulphuretted hydrogen. A similar reaction occurs with salts of bismuth, but the white precipitate becomes black on the addition of sulphuretted hydrogen (p. 713).

A solution of chloride of antimony gives with potash or soda

[1] It contained 1 in 100 in B.P. 1867. The original Donovan's Solution contained nearly 42 grains of each iodide in 10 fluid ounces.

a white precipitate which only dissolves in large excess, and with ammonia a white precipitate insoluble in excess. But if tartaric acid be present the precipitate dissolves in a slight excess of potash or soda, and with ammonia only a slight precipitate is formed.

General Actions of Antimony.—Salts of antimony probably combine with **albumen**, but in alkaline solutions they form no precipitate. They only form precipitates in acid solutions, and they consequently appear to exert an irritant action only on those parts of the animal body where they meet with an acid secretion, such as the orifices of the sweat-glands and of the stomach. When applied to the **skin** the chloride of antimony destroys the cuticle, and acts as a powerful escharotic, producing a deep slough and a slowly healing sore.

The other preparations, however, instead of affecting the whole surface to which they are applied, produce inflammation in isolated spots, which, beginning with papules, proceeds to pustules resembling those of small-pox. A similar pustular irritation is sometimes noticed upon the fauces of persons who have been taking antimony for some time, or have been poisoned by it. When taken **internally, small doses** produce little more than a feeling of warmth in the stomach and slightly increased diaphoresis, but larger doses cause loss of appetite, nausea accompanied by enfeeblement of the circulation, and a feeling of great depression and weakness. Not only the secretion of sweat, but those of the mucous membranes, stomach, intestine, and respiratory passages, seem at the same time to be considerably increased. In still **larger doses** antimony produces vomiting, with great depression of the circulation, and relaxation both of the voluntary and involuntary muscles. In large and **poisonous doses** it causes gastro-enteritis, with profuse diarrhœa and extreme collapse. The pulse is small and quick, the surface cold, and covered with clammy perspiration. There is great weakness and severe cramps of the extremities, and the symptoms somewhat resemble those of Asiatic cholera. **Death** may occur in this condition. It is sometimes preceded by delirium and convulsions, and tonic or clonic convulsive spasms.

The **treatment** of antimonial poisoning consists in the administration of tannin, and in some readily accessible form. The most easily obtained is a strong infusion of tea, and the tannin is more readily extracted from this by the addition of a small quantity of bicarbonate of sodium. Infusions of oak bark or of cinchona may also be used if obtainable. Milk and mucilaginous drinks may also be used. A diffusible stimulant should be given to counteract the collapse.

The mode in which tartar emetic causes **vomiting** has given rise to considerable dispute. It acts as an emetic even when injected into the veins, as well as when given by the stomach, and

it was found by Magendie that when the stomach of an animal was excised, and a pig's bladder filled with liquid attached to the lower end of the œsophagus, the injection of tartar emetic into the circulation caused movements of vomiting, and the contents of the bladder were expelled just as if the stomach had been *in situ.* This experiment seemed to prove not only that the act of vomiting was independent of the movements of the stomach itself, but also that tartar emetic caused vomiting by acting upon the vomiting centre, and not upon the stomach. The objection, however, has been raised that the action of the drug upon the vomiting centre is not direct, but reflex; and it has been urged that, although the stomach was removed, the antimony might still be carried by the circulation to the œsophagus and intestines, and by there causing irritation might produce reflex vomiting. This seems improbable, especially as the antimonial salts have a comparatively slight action on organs having, like the œsophagus and intestines, an alkaline reaction, instead of an acid one, as the stomach has.

It is probable, then, that tartar emetic does produce vomiting by its direct action on the vomiting centre in the medulla oblongata, but this direct action is not the only way in which it stimulates the vomiting centre—it also produces a reflex action upon it through the stomach. For it has been found that even when tartar emetic is injected into the veins, it is eliminated by the mucous membrane of the stomach (p. 38 *et seq.*), and may thus act upon that organ in the same way as when introduced directly into it. If its emetic action be due in any great measure to irritation of the stomach, one would expect that a smaller dose would be found sufficient to produce vomiting, when introduced directly into the stomach, than when injected into the veins, for in the former case the whole of it will come in contact with the stomach and will do so at once; in the latter case only a fraction of the quantity injected into the veins will reach the stomach, and some time will be required before it accumulates in the gastric mucous membrane sufficiently to cause irritation. This is exactly what is found by experiment, and vomiting is produced more quickly, and by a smaller dose, when the drug is introduced into the stomach, than when injected into the veins, just as we should expect to be the case if its emetic action were due in considerable measure to its action upon the stomach itself. This view is also supported by another experiment, for after the nervous channel by which impressions are conducted from the stomach to the vomiting centre is destroyed by section of the vagi, double the dose of the drug is required in order to produce vomiting. It may then be concluded that antimony acts chiefly as an emetic by irritating the stomach, and thus exciting the vomiting centre reflexly, but that it also acts directly on this centre when conveyed to it by the blood (p. 373).

When applied directly to the **heart** of a frog, it first increases, then slows, and finally arrests its pulsations in diastole. This action appears to be chiefly due to paralysis of the cardiac muscle itself, and possibly also to the effect upon motor ganglia.

The effect of antimony upon the **circulation** appears to depend partly upon the direct action of the drug upon the heart and vessels, and partly on its reflex action upon them through the nerves of the stomach. In warm-blooded animals the pulse becomes quicker as the feeling of nausea increases, and, after the vomiting, again falls nearly to the normal. Its volume is at the same time diminished. After the nausea has ceased, the pulse again becomes quicker, and after this secondary acceleration has reached a greater or less height, according to the dose, it again sinks to the normal.

As the primary acceleration during the stage of nausea ceases with vomiting, it is probably to be attributed to reflex irritation of the accelerating centres, or reflex depression of the vagus through the gastric nerves, whereas the cause of the secondary acceleration is more probably to be sought in diminished power of the vagus nerve itself. The **blood-pressure** sinks constantly from the very beginning, and this sinking is probably due to diminished power of the cardiac pulsations. The **temperature** in the extremities appears to be diminished during the stage of nausea, owing to the smaller amount of blood going to them. As less blood reaches the surface in this condition, there is less opportunity afforded for its being cooled by contact with the atmosphere, and the temperature in the body gradually rises, even above the normal. When the spasm of the vessels in the extremities relaxes, they also become warmer than normal. As the effects pass off, the temperature sinks to the normal or below it.

The **respiration** is first increased, and then diminished.

Large doses of antimony affect the **spinal cord** both in cold- and warm-blooded animals. It appears to paralyse, after, perhaps, slightly exciting, both the sensory and motor tracts of the spinal cord, and as this paralysis appears in frogs while the heart still continues to beat, it must be due to the direct action of the drug upon the nervous system itself, and not to its indirect action through the circulation. The **motor** and **sensory nerves** appear also to be paralysed. The **muscles** are weakened (p. 127).

When given for a length of time, antimony seems to produce **fatty degeneration** of various organs.

The action of antimony upon the **skin** in frogs is even more rapid than that of arsenic (p. 716), and differs from it in this respect, that the softening does not affect the cells of the columnar layer only, but extends to those of the intermediate layer (Fig. 172). In consequence of this, the cuticle does not merely become

detached from the dermis and peel off in strips as in poisoning by arsenic, but the cells of the epidermis becoming detached

FIG. 172.—Vertical section of epidermis from a frog poisoned by antimony. *a*, Columnar layer in which large cavities are formed. *b*, Columnar cells in which the reduced protoplasm is drawn into processes. *c*, Spaces in the intermediate layer. *d*, Light lines between cells indicating a softening and separation of cells. (After Nunn.)

from each other, the cuticle becomes converted into a soft jelly-like mass which can be scraped or brushed off.

Tartar emetic appears to be **eliminated** by the mucus of the stomach and alimentary canal, by the bile, and by the kidneys. Its action upon the renal secretion is somewhat uncertain. It appears to increase urea, uric acid, and pigment, and to diminish the water and the chloride of sodium, probably by increasing the perspiration.

USES.—The local uses of antimony will be considered under the special preparations.

When antimony is given **internally** for its action on the system generally, tartar emetic is the preparation usually employed, but the other preparations of antimony have a similar action when given in appropriate doses. It can be used for its emetic action, nauseant and depressant action, or diaphoretic action. As an **emetic** it has been employed in cases of croup, in order to cause expulsion of the false membrane; but for this purpose other emetics, such as ipecacuanha, alum, or sulphate of zinc, are now more generally employed, as they do not cause so much depression. It has also been used with considerable success to cut short an attack of intermittent fever, either alone or combined with a purgative. Indeed, in cases where malarial poisoning has been intense, quinine sometimes proves ineffectual unless preceded by the administration of an emetic and purgative. It has sometimes been injected into the veins to produce vomiting, in cases of obstruction of the œsophagus, as, for example, by a piece of meat firmly lodged in it, and to cause expulsion of a biliary calculus lodged in the gall-duct, by the pressure from behind which the movements of vomiting produce, along with the relaxation of the muscular fibres of the gall-duct itself.

When large doses are administered several times, what is termed **tolerance** of the drug sets in, and it no longer produces vomiting. It has been used in this way in pneumonia, but the plan is now rarely followed. How this tolerance is produced is

not at present understood. It is not improbable that it may be caused by the irritant action of the first few doses upon the stomach arresting the secretion of the acid juice, and producing a condition similar to that which occurs in fever. In this condition subsequent doses of the tartar emetic, meeting with no acid, will have but a feeble action upon the stomach.

In cases of obstinate constipation it has been used along with sulphate of magnesium. As a **nauseant** it has been given to relax the cervix uteri in labour; in acute inflammations, e.g. in acute orchitis, where the emetic is first given, and nausea is kept up by a continued administration of smaller doses; and also in pericarditis, pneumonia, pleurisy, peritonitis, meningitis, bronchitis, and hepatitis, as well as in acute rheumatism. As an **expectorant** it is used in bronchitis. The cases in which it is especially serviceable are those in which there is great congestion and much dyspnœa, with little or no secretion, as shown by loud, sibilant *râles* over the chest, the pulse being full, and the face flushed, with a tendency to lividity. It has also been given to check hæmoptysis when there is much excitement of the circulation. As a **sedative** it is of use in nervous diseases, attended with much excitement, such as certain cases of insanity, delirium tremens, and puerperal convulsions. In the delirium of fever, it has been highly recommended by Dr. Graves, in combination with opium, as a means of producing sleep. Where the delirium is furious the tartar emetic must be given in full, and the opium in small doses; while if the delirium is milder and the sleeplessness great, the opium dose must be increased and that of the tartar emetic diminished. The same treatment may be adopted in the delirium and sleeplessness of delirium tremens.

For its **diaphoretic** action, antimony has been used to arrest commencing inflammations, such as catarrh, and to check febrile conditions. For this purpose it is not unfrequently given as tartar emetic in doses of $\frac{1}{16}$ grain frequently repeated, or as James's powder. In acute dropsy it appears to be occasionally useful, especially as a diaphoretic, in combination with bitartrate of potassium and squills.

PREPARATIONS CONTAINING ANTIMONY.

B.P.	U.S.P.
Antimonii Oxidum.	Antimonii et Potassii Tartras.
Antimonium Nigrum Purificatum.	,, Oxidum.
,, **Sulphuratum.**	Antimonii Sulphidum.
,, **Tartaratum.**	,, ,, Purificatum.
Liquor Antimonii Chloridi.	,, Sulphuratum.
Pilula Hydrargyri Subchloridi Composita (*v.* p. 522).	Pilulæ Antimonii Compositæ (p. 523).
Pulvis Antimonialis.	Pulvis Antimonialis.
Unguentum Antimonii Tartarati.	Syrupus Scillæ Compositus.
Vinum Antimoniale.	Vinum Antimonii.

U.S.P. Antimonii Sulphidum. SULPHIDE OF ANTIMONY.—Native sulphide of antimony, Sb_2S_3; 340; purified from siliceous matter by fusion, and as nearly free from arsenic as possible.

CHARACTERS.—Steel-grey masses of a metallic lustre, and a striated crystalline fracture without taste or smell.

U.S.P. PREPARATION.

Antimonium Sulphidum Purificatum.

This is the ore from which the other compounds are prepared.

It seems to be inert, and is not used internally.

Antimonium Nigrum Purificatum, B.P.; Antimonii Sulphidum Purificatum, U.S.P. BLACK ANTIMONY, B.P.; PURIFIED SULPHIDE OF ANTIMONY, U.S.P. Sb_2S_3; 340.

CHARACTERS.—A greyish-black crystalline powder, without smell or taste.

SOLUBILITY.—It is insoluble in water or alcohol.

REACTIONS.—It dissolves almost entirely in boiling hydrochloric acid, evolving sulphuretted hydrogen, and the solution affords a white precipitate when poured into water.

PREPARATION.—The crude sulphide, purified by fusion, is obtained in very fine powder by elutriation, then digested with ammonia to remove arsenic, washed and dried.

IMPURITIES.—Other sulphides and arsenic.

TESTS.—If one grain be dissolved in hydrochloric acid, and the solution, slightly diluted, be gently warmed with a piece of bright copper foil, the copper being washed, dried, and heated in a dry narrow test-tube, no crystalline sublimate (of arsenious anhydride) should form on the upper cool part of the tube.

PREPARATIONS.

B.P.	U.S.P.
Antimonium Sulphuratum.	Antimonium Sulphuratum.
Liquor Antimonii Chloridi.	

Antimonium Sulphuratum, B. and U.S.P. SULPHURATED ANTIMONY.

B.P. Sulphide of antimony, Sb_2S_3; 336; with a small and variable amount of oxide of antimony, Sb_2O_3.

U.S.P. Chiefly antimonious sulphide, Sb_2S_3; 340; with a very small amount of antimonious oxide.

CHARACTERS.—B.P. An orange-red powder. U.S.P. A reddish-brown, amorphous powder, odourless and tasteless.

SOLUBILITY.—It is insoluble in water and in alcohol.

REACTIONS.—B.P. It is readily dissolved by caustic soda, also by hydrochloric acid with the evolution of sulphuretted hydrogen and the separation of sulphur. Sixty grains, moistened and warmed with successive portions of nitric acid until red fumes cease to be evolved, and then dried and heated to redness, give a white residue weighing about 40 grains.

U.S.P. When heated with twelve parts of hydrochloric acid, it is nearly all dissolved, with evolution of sulphuric acid. The residue, after having been washed and dried, burns, on the application of a flame, with the characteristic

odour of sulphur, and should leave not more than a scanty ash. On dropping a solution of sulphurated antimony in hydrochloric acid into water, a white precipitate is produced, which, after washing and drying, should weigh not less than 85 per cent. of the sulphide. The liquid filtered from this precipitate yields an orange-red precipitate with hydrosulphuric acid.

Distilled water boiled with sulphurated antimony, filtered and acidulated with hydrochloric acid, should be rendered not more than slightly opalescent by test solution of chloride of barium (limit of sulphate).

Preparation.—By boiling black antimony with caustic soda and sulphur, the sulphide is partly converted into oxide and partly unites with sodium, forming sulphantimonite and antimonite of sodium.

$$\overset{\text{Sulphide of Antimony}}{2Sb_2S_3} + \overset{\text{Soda}}{6NaHO} = \overset{\text{Sulphantimonite of Sodium}}{2Na_3SbS_3} + \overset{\text{Antimonious Oxide}}{Sb_2O_3} + 3H_2O,$$

and

$$\overset{\text{Antimonious Oxide}}{Sb_2O_3} + \overset{\text{Soda}}{6NaHO} = \overset{\text{Antimonite of Sodium}}{2Na_3SbO_3} + 3H_2O.$$

Owing to the presence of free sulphur, sulphantimoniate, and antimoniate of sodium are also formed.

$$\overset{\text{Sulphide of Antimony.}}{2Sb_2S_3 + S_2} + \overset{\text{Soda}}{6NaHO} = \overset{\text{Sulphantimoniate of Sodium}}{2Na_3SbS_4} + \overset{\text{Antimonic Oxide}}{Sb_2O_5} + 3H_2O,$$

and

$$\overset{\text{Antimonic Oxide}}{Sb_2O_5} + \overset{\text{Soda}}{6NaHO} = \overset{\text{Antimoniate of Sodium}}{2Na_3SbO_4} + 3H_2O.$$

The sulphides and oxides of antimony are soluble in the solutions of the salts of antimony just mentioned. The addition of sulphuric acid decomposes the salts, with the formation and precipitation of the oxides and sulphides. In order to ensure uniformity of the product the acid is added while the solution is hot.

These antimony compounds are soluble in caustic soda, but when this is neutralised they are precipitated, the greater part of them being decomposed and the Sb_2O_3 reconverted into Sb_2S_3.

$$\overset{\text{Sulphantimonite of Sodium}}{2Na_3SbS_3} + \overset{\text{Sulphuric Acid}}{3H_2SO_4} = \overset{\text{Sodium Sulphate}}{3Na_2SO_4} + \overset{\text{Antimonious Sulphide}}{Sb_2S_3} + \overset{\text{Sulphuretted Hydrogen}}{3H_2S}.$$

$$\overset{\text{Antimonite of Sodium}}{2Na_3SbO_3} + 3H_2SO_4 = 3Na_2SO_4 + \overset{\text{Antimonious Oxide}}{Sb_2O_3} + \overset{\text{Water}}{3H_2O}.$$

$$\overset{\text{Sulphantimoniate of Sodium}}{2Na_3SbS_4} + 3H_2SO_4 = 3Na_2SO_4 + \overset{\text{Antimonic Sulphide}}{Sb_2S_5} + 3H_2S.$$

$$\overset{\text{Antimoniate of Sodium}}{2Na_3SbO_4} + 3H_2SO_4 = 3Na_2SO_4 + \overset{\text{Antimonic Oxide}}{Sb_2O_5} + 3H_2O.$$

Dose.—1 to 5 grains.

Preparations.

B.P.	DOSE.
Pilula Hydrargyri Subchloridi Composita (Plummer's pill) (p. 522)..............................1 part in 5..................................	5–10 gr.

U.S.P.

Pilulæ Antimonii Compositæ (Plummer's pill) (p. 523)....1 part in 4.....1 or 2 pills.

The oxide it contains is probably the active part, and as this is variable the action is rather uncertain.

Liquor Antimonii Chloridi, B.P. SOLUTION OF CHLORIDE OF ANTIMONY.

CHARACTERS.—A heavy liquid, usually of a yellowish-red colour.

REACTIONS.—A little of it dropped into water gives a white precipitate, and the filtered solution lets fall a copious deposit on the addition of nitrate of silver. If the white precipitate formed by water be treated with sulphuretted hydrogen it becomes orange-coloured. The specific gravity of the solution is 1·47. One fluid drachm of it mixed with a solution of a quarter of an ounce of tartaric acid in four fluid ounces of water, forms a clear solution, which, if treated with sulphuretted hydrogen, gives an orange precipitate, weighing, when washed and dried at 212° F., at least 22 grains.

PREPARATION.—By boiling black antimony with hydrochloric acid, $Sb_2S_3 + 6HCl = 2SbCl_3 + 3H_2S$.

PREPARATION IN WHICH SOLUTION OF CHLORIDE OF ANTIMONY IS USED.

Antimonii Oxidum.

USES.—Is a powerful **caustic**—sometimes applied to cancers and to poisoned wounds.

Antimonii Oxidum, B. and U.S.P. OXIDE OF ANTIMONY. Sb_2O_3; 288.

CHARACTERS.—A greyish-white powder, fusible at a low red-heat.

SOLUBILITY.—It is insoluble in water, but readily dissolved by hydrochloric acid.

REACTIONS.—The solution, dropped into distilled water, gives a white deposit, at once changed to orange by sulphuretted hydrogen. It dissolves entirely when boiled with an excess of the acid tartrate of potassium.

PREPARATION.—By pouring solution of chloride of antimony into water and treating the precipitate of oxychloride with sodium carbonate.

$$\underset{\text{Chloride of Antimony}}{12SbCl_3} + 15H_2O = \underset{\text{Oxychloride of Antimony}}{2SbCl_3, 5Sb_2O_3} + \underset{\text{Hydrochloric Acid}}{30HCl.}$$

$$\underset{\text{Oxychloride of Antimony}}{2SbCl_3,5Sb_2O_3} + \underset{\text{Carbonate of Sodium}}{3Na_2CO_3} = \underset{\text{Oxide of Antimony}}{6Sb_2O_3} + \underset{\text{Sodium Chloride}}{6NaCl} + 3CO_2.$$

DOSE.—1 to 4 grains.

PREPARATIONS.

B. AND U.S.P.	DOSE.
Pulvis Antimonialis. Antimonial powder or James's powder (one part of oxide of antimony with two of phosphate of calcium).........	3–10 grs.

USES —Oxide of antimony may be used for the same purposes as tartar emetic, but it is not soluble in water, and it depends very much on the state of the stomach how much of it will be dissolved. It is therefore less certain in its action than tartar emetic and the latter is consequently to be preferred. In consequence of its insolubility it is said to be slower and milder than tartar emetic, but this advantage is more than counterbalanced by its uncertainty.

James's powder is given as an antipyretic in fever and rheumatism. It is also given in chronic skin-diseases along with mercury.

Antimonium Tartaratum, B.P.; Antimonii et Potassii Tartras, U.S.P. TARTARATED ANTIMONY, TARTAR EMETIC, B.P.; TARTRATE OF ANTIMONY AND POTASSIUM, U.S.P.

$KSbC_4H_4O_7.H_2O$, B.P.; $2KSbOC_4H_4O_6.H_2O$; 664, U.S.P.—A tartrate of potassium and antimony.

CHARACTERS.—In colourless transparent crystals exhibiting triangular facets.

SOLUBILITY.—It is soluble in water, and less so in proof spirit.

REACTIONS.—It decrepitates and blackens upon the application of heat (tartrate). Its solution in water gives with hydrochloric acid a white precipitate, soluble in excess, and which is not formed if tartaric acid be previously added.

PREPARATION.—By boiling acid tartrate of potassium and oxide of antimony together, $2KHC_4H_4O_6 + Sb_2O_3 = 2K(SbO)C_4H_4O_6 + H_2O$.

DOSE.—As a diaphoretic $\frac{1}{16}$ to $\frac{1}{6}$th of a grain; as an emetic, 1 to 2 grains. Of the wine as a diaphoretic, 10 to 40 min.; as an emetic for children, $\frac{1}{2}$ to 1 fl. dr. repeated frequently.

PREPARATIONS.

B.P.	STRENGTH.	DOSE.
Unguentum Antimonii Tartarati (with simple ointment.)	1 part in 5	
Vinum Antimoniale. Antimonial Wine	2 gr. in 1 fl. oz. of sherry	5 min.–1 fl. dr.

U.S.P.	STRENGTH.	DOSE.
Syrupus Scillæ Compositus		5 min.–1 fl. dr.
Vinus Antimonii. Wine of Antimony	4 parts in 60 of water and stronger white wine up to 1,000.	

USE.—This preparation of antimony is readily soluble, and as the proportion of the dose administered which actually takes effect is more constant than that of the other preparations of antimony, it has gradually displaced them. For its uses *vide* p. 725.

Tartar emetic ointment has been used as a **counter-irritant** in cases of neuralgia, paralysis of children, enlarged joints, acute meningitis, laryngitis, acute bronchitis, whooping-cough, phthisis, asthma, angina pectoris, and subacute ovaritis. For many of these purposes the application of iodine preparations is now preferred.

BISMUTH. Bi; 210.

Bismuth forms three classes of compounds in which it is bi-, tri-, and quinqui-valent respectively.

GENERAL SOURCES.—It is found native in the metallic state.

GENERAL REACTIONS.—It is distinguished by the white precipitate which falls on throwing a solution of the nitrate or chloride into water, and the blackening of this by sulphuretted hydrogen (*vide* p. 713).

GENERAL PREPARATION OF SALTS OF BISMUTH.

Salt	Prepared from	By
Subnitrate, B. and U.S.P.	Bismuth . . .	Dissolving in nitric acid, throwing the solution into a large quantity of water, collecting and drying the precipitate.
Carbonate, B.P.; Subcarbonate, U.S.P.	Ditto . . .	Dissolving in nitric acid, evaporating to a small bulk and adding to solution of ammonium carbonate.
Oxide, B.P. . .	Subnitrate . .	Boiling with solution of soda.
Citrate, B. and U.S.P.	Ditto . .	B.P. Dissolving in nitric acid, and adding freshly-made citrate of sodium. U.S.P. Boiling with citric acid and washing with a large quantity of water, when insoluble citrate is formed.
Citrate of bismuth and ammonium, B. and U.S.P.	Citrate of bismuth .	Mixing the citrate to a smooth paste with water and adding ammonia until it is dissolved and the liquid is neutral or faintly alkaline; filtering, evaporating, and drying.
Solution of citrate of bismuth and ammonium, B.P.	Ditto .	Do., and diluting instead of evaporating.

GENERAL ACTION.—The soluble salts of bismuth, such as the citrate of bismuth and ammonium, when given in large doses have an action like that of antimony or arsenic and cause gastro-enteritis with fatty degeneration of the liver. Small doses of soluble preparations, or larger doses of sparingly soluble preparations, have a sedative effect on the stomach like that of minute doses of arsenic. The subnitrate is so sparingly soluble that its utility in gastric catarrh is probably due to its mechanical action, like charcoal (p. 542) or binoxide of manganese.

USES.—Subnitrate of bismuth is used under the name of Spanish or pearl white to whiten the complexion, and as a dusting powder, lotion, or ointment to chapped nipples and hands, abraded surfaces and chronic oozing from the skin, as eczema, in order to take up moisture and allay smarting and itching.

It has also been employed externally as an application in scaly diseases, and in intertrigo in combination with starch and boric or salicylic acid. From its power of diminishing the irritability of mucous membranes it was applied by Ferrier, along with morphine in the form of a snuff,[1] to arrest nasal catarrh, and has been used as an injection in ozæna, leucorrhœa, and gonorrhœa, to diminish the irritability. In powder with morphine and starch it is a useful insufflation in laryngeal phthisis and other painful laryngeal affections. It is applied as a local

[1] Bismuth subnitrate 6 drachms; hydrochlorate of morphine 2 grains; powdered acacia 2 drachms.

sedative to diminish the pain, nausea, or vomiting in irritable dyspepsia, and to lessen the irritability of the intestine in diarrhœa and dysentery. It is very serviceable, either alone or combined with lime or alkalis in the gastro-intestinal catarrh caused by cold, which is commonly known as cold in the stomach, as well as in the same affection occurring in children at the period of dentition.

It is useful in pyrosis, gastralgia, and vomiting, whether the vomiting be from ulcer of the stomach or other causes. It acts remarkably well in the indigestion and pain in the stomach caused by the use of alcohol. In such cases it is best given with a little magnesia, about ten grains of the subnitrate with an equal quantity of magnesia or its carbonate.

The carbonate of bismuth is more soluble in the gastric juice than the subnitrate, and is supposed to be more powerful, and the same advantage, if advantage it be, is possessed by the citrate of bismuth and ammonium. My own experience leads me to prefer the less soluble subnitrate to either of the other preparations.

B.P. Bismuthum. BISMUTH.—A crystalline metal. In its crude state it is impure.

PREPARATION.

Bismuthum Purificatum.

B.P. Bismuthum Purificatum. PURIFIED BISMUTH.

CHARACTERS.—A crystalline metal of a greyish-white colour, with a distinct roseate tinge. Specific gravity 9·83.

SOLUBILITY AND REACTIONS.—Dissolved in a mixture of equal volumes of nitric acid and distilled water, it forms a solution which by evaporation yields colourless crystals, that are decomposed on the addition of water, giving a white precipitate.

PREPARATION.—By fusing with cyanide and carbonate of potassium, carbonate of sodium and sulphur.

IMPURITIES.—Arsenic, iron, copper, cadmium, lead, antimony.

TEST.—If the mother liquor from which the crystals have been separated be evaporated with hydrochloric acid until all the nitric acid is dissipated, a little of the product yields no evidence of arsenium on being examined by the hydrogen test commonly known as Marsh's Test; no blue coloration on adding water and excess of ammonia (no copper), and no precipitate on filtering and saturating the ammoniacal filtrate with nitric acid (no tin or cadmium); no white precipitate with diluted sulphuric acid (no lead); no red or black precipitate with sulphite of sodium (no selenium nor tellurium); no blue precipitate with ferrocyanide of potassium (no iron).

PREPARATIONS CONTAINING BISMUTH.

B.P.	U.S.P.
Bismuthi Carbonas.	Bismuthi Carbonas.
" Subnitras.	" Citras.
Liquor Bismuthi et Ammonii Citratis.	" Subnitras.
Trochisci Bismuthi.	

Bismuthi Subnitras, B. and U.S.P. SUBNITRATE OF BISMUTH. $BiONO_3.H_2O$; 306, U.S.P.

CHARACTERS.—A heavy white powder in minute crystalline scales, blackened by sulphuretted hydrogen.

SOLUBILITY.—Insoluble in water, but soluble in nitric acid mixed with half its volume of distilled water.

REACTIONS.—The solution in nitric acid when poured into water gives a white precipitate. It forms with sulphuric acid diluted with an equal bulk of water a solution which is blackened by sulphate of iron (nitrate). The nitric acid solution gives no precipitate with diluted sulphuric acid (no lead) nor with solution of nitrate of silver (no chloride).

IMPURITIES.—Lead, nitrates, chlorides.

DOSE.—5 to 20 grains.

PREPARATION.

B.P.	DOSE.
Trochisci Bismuthi, 2 grs. in each lozenge	1 to 6 lozenges.

Bismuthi Carbonas, B.P.; Bismuthi Subcarbonas, U.S.P. CARBONATE OF BISMUTH, B.P.; SUBCARBONATE OF BISMUTH, U.S.P. $2(Bi_2CO_3).H_2O$, B.P.; $(BiO)_2CO_3.H_2O$; 530, U.S.P.

CHARACTERS.—A white powder, blackened by sulphuretted hydrogen.

SOLUBILITY.—It is insoluble in water, but soluble with effervescence in nitric acid.

REACTIONS.—The solution gives the reactions of bismuth (pp. 713, 731).

IMPURITIES.—Nitrate.

TEST.—When added to sulphuric acid coloured with sulphate of indigo the colour of the latter is not discharged.

DOSE.—5 to 20 grains.

Bismuthi Citras, B. and U.S.P. CITRATE OF BISMUTH. $BiC_6H_5O_7$; 399.

CHARACTERS.—A white amorphous powder, permanent in the air, odourless and tasteless.

SOLUBILITY.—It is insoluble in water or alcohol, but soluble in water of ammonia.

DOSE.—2 to 5 grains.

USES.—Used to prepare the solution of bismuth and ammonium.

PREPARATIONS.

B.P.	U.S.P.
Liquor Bismuthi et Ammonii Citratis.	Bismuthi et Ammonii Citras. Liquor „ Citratis.

B.P. Liquor Bismuthi et Ammonii Citratis. SOLUTION OF CITRATE OF BISMUTH AND AMMONIUM.

CHARACTERS.—A colourless solution with a saline and slightly metallic taste. Neutral or slightly alkaline to test-paper; mixing with water without change. One fluid drachm contains 3 grains of oxide of bismuth.

REACTIONS.—It gives the reactions of ammonia and bismuth.

DOSE.—$\frac{1}{2}$ to 1 fluid drachm.

B. and U.S.P. Bismuthi et Ammonii Citras. CITRATE OF BISMUTH AND AMMONIUM.

CHARACTERS.—Small, shining, pearly or translucent scales, becoming opaque on exposure to air, odourless, having a slightly acidulous and metallic taste, and a neutral or faintly alkaline reaction.

REACTIONS.—The aqueous solution of the salt gives the reaction of bismuth, of ammonia (p. 634) and of a citrate (p. 594).

DOSE.—2 to 4 grains.

USES.—The solution of bismuth and ammonium, B.P., and the soluble salt, U.S.P., are more astringent and irritant in their action than the insoluble subnitrate, oxide, or carbonate. They may be used as astringents, but are inferior to the insoluble preparations as a means of allaying irritation.

CHAPTER XXVIII.

METALS—(*continued*).

Class VIII

Group I.

Iron—*Nickel*—*Cobalt*—Manganese.

FERRUM; IRON. Fe; 55·9.

Metallic iron in the form of fine, bright, and non-elastic wire.

Iron forms ferrous salts in which it is bivalent, e.g. $FeCl_2$ or $FeSO_4$, and ferric, in which it is either trivalent or quadrivalent. Ferric chloride may be regarded as $FeCl_3$ or as Fe_2Cl_6, in which each of two atoms of quadrivalent iron have one affinity saturated by union with each other, and the other three by chlorine, $Cl_3{\equiv}Fe{-}Fe{\equiv}Cl_3$.

General Sources.—It is found native in the metallic state, and also as oxide, sulphide, chloride, carbonate, phosphate, sulphate, and arseniate. It is obtained from its ores by smelting with coke and clay or limestone.

General Reactions.—These are shown in the accompanying table. The reactions most generally mentioned in the pharmacopœias are those with ferrocyanide and ferricyanide of potassium. It is to be remembered that a preparation of iron containing it in both the ferrous and ferric condition, or which, by its decomposition, yields iron in these two states, gives a precipitate with both of these reagents. The arseniate of iron, B.P., phosphate of iron, and the citrate of iron and quinine are examples of this.

General Reactions of Iron Salts.

Reagent	Ferrous Salts	Ferric Salts
Hydrogen sulphide .	No precipitate .	White precipitate of sulphur (the ferric are reduced to ferrous).
Ammonium sulphide	Black precipitate .	Black precipitate.
Caustic alkalis and ammonia	Nearly white precipitates of ferrous hydrate rapidly becoming green and then brown	Foxy-red precipitates of ferric hydrate.
Carbonates of ditto .	Whitish precipitate of ferrous carbonate which changes like the hydrate .	Foxy-red precipitates. Carbonic acid escapes.
Potassium ferrocyanide	Nearly white precipitate becoming blue on exposure	Deep blue precipitate (Prussian blue).[1]
Potassium ferricyanide	Deep blue precipitate	No precipitate. Dark coloration.
Tincture of galls .		Intense black.

General Impurities.—Zinc, copper, and fixed alkalis may be present in its salts. Ferrous salts may be present as impurities in ferric and *vice versâ*.

Tests.—The test used for the chloride in the U.S.P. is as follows :—If the iron be completely precipitated from a solution of the salt by an excess of water of ammonia the filtrate should not yield either a white precipitate (absence of zinc) or a dark-coloured precipitate with hydrosulphuric acid (absence of copper), nor should it leave a fixed residue on evaporation and gentle ignition.

The absence of ferrous salts as impurities in ferric is ascertained by the solution giving no precipitate with *ferri*cyanide of potassium.

The absence of ferric salts as an impurity in ferrous is ascertained by the precipitate with *ferro*cyanide of potassium not being blue at first, but nearly white, and only becoming blue on exposure.

General Preparation of Salts of Iron.

	Prepared from	By
Ferrous Sulphate (p. 741)	Iron . . .	Dissolving in sulphuric acid.
Dried Sulphate (p. 741)	Ferrous sulphate .	Heating to drive off water of crystallisation.
Granulated Sulphate, B.P., Precipitated, U.S.P. (p. 741)	Ditto . . .	Pouring an aqueous solution into spirit.
Carbonate (Saccharated) (p. 742)	Ditto . . .	Decomposing (by ammonium carbonate, B.P.), (by sodium bi-carbonate, U.S.P.), and mixing with sugar.
Do. (Mistura Ferri Composita) (p. 742)	Ditto . . .	Decomposing by potassium carbonate and mixing with myrrh, &c.

[1] With the tartrate of iron and ammonium (U.S.P.) no colour or precipitate is produced unless the solution is acidulated with hydrochloric acid.

General Preparation of Salts of Iron—*continued.*

	Prepared from	By
Ferric Sulphate, B.P. (p. 742) Ferric Tersulphate, U.S.P. (p. 742)	Ferrous sulphate	Adding sulphuric acid and oxidising by heating with nitric acid. ($6FeSO_4 + 3H_2SO_4 + 2HNO_3 = 3Fe_2(SO_4)_3 + 4H_2O + N_2O_2$.)
Ferric Subsulphate, U.S.P. (p. 743)	Ferrous sulphate	Ditto, using too little sulphuric acid to form tersulphate.
Ferric Oxide (p. 743)	Ferric sulphate .	Mixing with magnesia and water, U.S.P. Mixing with water and solution of soda, B.P.
Ferric Oxide (Hydrated, U.S.P.) (p. 743)	Ditto . . .	By precipitating with ammonia, washing and making into a paste with water, U.S.P.
Ferric Oxide (Hydrated, B.P.) (p. 744)	Ditto . . .	Pouring the diluted solution into solution of soda, B.P.; and drying below 212°.
Reduced Iron (p. 744)	Ferric oxide . .	Passing hydrogen over it while heated ($Fe_2O_3 + 6H = Fe_2 + 3H_2O$).
Ferric Chloride (p. 745)	Iron . . .	Dissolving in hydrochloric acid and oxidising by nitric acid. ($3Fe_2 + 12HCl = 6FeCl_2 + 12H$ $6FeCl_2 + 6HCl + 2HNO_3 = 3Fe_2Cl_6 + 4H_2O + N_2O_2$.)
Ferric Nitrate (p. 747)	Iron . . .	Dissolving in nitric acid ($Fe_2 + 8HNO_3 = Fe_2(NO_3)_6 + 4H_2O + N_2O_2$).
Ferric Oxychloride (Dialysed Iron) B.P. (p. 746)	Ferric chloride .	Precipitating ferric oxide by ammonia, dissolving it in solution of perchloride, and dialysing the solution until it is tasteless.
Ferric Acetate (Solution of), B. and U.S.P. (p. 744)	Ferric sulphate .	Precipitating ferric oxide by ammonia, washing, and dissolving in glacial acetic acid, and diluting to the necessary strength.
Ferric Citrate, U.S.P. (p. 748)	Ditto (Tersulphate)	Precipitating oxide by ammonia, washing and dissolving in citric acid. This forms the Liquor Ferri Citratis, U.S.P. Ferri Citras is prepared by evaporation of the Liquor under 60° C.
Tartrate of iron and potassium, U.S.P. (Ferrum Tartaratum, B.P.) (p. 747)	Persulphate . .	Precipitating ferric oxide by ammonia, washing and mixing with acid tartrate of potassium.
Tartrate of iron and ammonium, U.S.P. (p. 747)	Ditto . . .	Ditto, using tartaric acid and tartrate of ammonium in place of acid tartrate of potassium.
Citrate of iron and ammonium, B. and U.S.P. (p. 748)	Ditto . . .	Ditto, using citric acid and ammonia.
Citrate of iron and quinine, B. and U.S.P. (p. 749)	Ditto and sulphate of quinine	Precipitating ferric oxide and quinine by ammonia and dissolving it in citric acid.
Citrate of iron and strychnine, U.S.P. (p. 749)	Ferric sulphate and strychnine	Precipitating ferric oxide by ammonia and dissolving it along with strychnine in citric acid.
Sulphate of iron and ammonium, U.S.P. (p. 749)	Ferric sulphate and ammonium sulphate	Heating them together.

General Preparation of Salts of Iron—*continued.*

	Prepared from	By
Ferrous Lactate, U.S.P. (p. 750)	Iron	Dissolving in lactid acid.
Ferrous Oxalate, U.S.P. (p. 750)	Ferrous sulphate .	Precipitating a solution with oxalic acid (ferrous oxalate is very slightly soluble).
Ferrous Iodide, B.P. (Syrup of) (p. 750)	Iron	Heating with iodine and water (the completion of the process is recognised by the brown colour of the iodine disappearing and the froth becoming white) and then adding syrup.
Ferrous Iodide (Pill of), B.P. (p. 750)	Ditto . . .	Same as syrup, but mixing with sugar and powdered liquorice root instead of with syrup.
Ferrous Bromide (Syrup of) U.S.P. (p. 751)	Ditto . . .	Same as syrup of iodide, using bromine instead of iodine.
Arseniate of Iron, B.P. (p. 751)	Ferrous sulphate, arseniate of sodium, and acetate of sodium	Mixing a solution of arseniate and acetate of sodium with one of ferrous sulphate. If arseniate of sodium alone were used, free sulphuric acid would be formed, which would react on the arseniate. $3FeSO_4 + 2Na_2HAsO_4 = Fe_3As_2O_8 + 2Na_2SO_4 + H_2SO_4$. To avoid this acetate of sodium is added. The sulphuric acid combines with the sodium and sets free acetic acid, which has no action on the arseniate of iron. $3FeSO_4 + 2Na_2HAsO_4 + 2NaC_2H_3O_2 = Fe_3As_2O_8 + 3Na_2SO_4 + 2HC_2H_3O_2$.
Phosphate of Iron, B. and U.S.P. (p. 751)	Ferrous sulphate, phosphate of sodium, and acetate of sodium	The same process as in the preparation of arseniate. The reactions are similar. $3FeSO_4 + 2Na_2HPO_4 + 2NaC_2H_3C_2 = Fe_3P_2O_8 + 3Na_2SO_4 + 2HC_2H_3O_2$.
Pyrophosphate of Iron, U.S.P. (p. 752)	Citrate of iron . .	Decomposing solution by solution of sodium pyrophosphate.
Hypophosphite of Iron, U.S.P. (p. 752)	Ferrous sulphate .	Decomposing by hypophosphite of calcium when ferrous hypophosphite is precipitated, but on evaporation becomes ferric.
Valerianate of Iron, U.S.P. (p. 752)	Ferric sulphate .	Decomposing by valerianate of sodium.

General Action of Iron Salts.—Iron differs from most of the other heavy metals in forming a normal constituent of the animal body, so that it may be regarded as a food as well as a medicine. It forms an important constituent of the hæmoglobin in the blood. This acts as the oxygen-carrier to the tissues, and, therefore, the tissue-oxidation and the functional activity of the organs depend more or less upon the amount of iron present in the body. According to Preyer, in a healthy woman the minimum amount of

iron in 100 grammes of blood is ·048 gramme, of hæmoglobin 11·57 grammes; the maximum, ·057 gramme and 13·69 grammes of iron and hæmoglobin respectively. In a healthy man, in 100 grammes the proportion is ·0508 gramme of iron (minimum), ·063 (maximum), 12·09 grammes hæmoglobin (minimum), and 15·07 grammes (maximum).[1] Both per- and proto-salts of iron form compounds with **albumen,** but they differ in their properties. The ferrous salts give a yellow colour with albuminous solutions, but do not precipitate them, the albuminous compound being, apparently, usually soluble. Diluted ferric salts, on the contrary, precipitate albumen slowly, and concentrated solutions precipitate it rapidly. The precipitate is soluble in dilute acids and in gastric juice.

When applied to the **skin** neither ferrous nor ferric salts have any action, as they do not dissolve the epidermis nor pass through it in any appreciable quantity. When applied to a denuded surface, or to a mucous membrane they combine with albumen. The ferrous salts have but a slight astringent action, whereas the ferric salts coagulate the albumen on the surface and also blood. They are thus powerful astringents and styptics. In the **mouth** they all have an inky taste, and as they are liable to form black sulphides with sulphuretted hydrogen, which is not unfrequently present in the breath, they are apt to discolour the teeth or tongue. In the **stomach** they have an astringent and irritant action, that of the ferric being more powerful than that of the ferrous salts. In the **intestine** they have a somewhat similar action; meeting here, as they often do, with sulphuretted hydrogen they become converted, in great part, into sulphides, and, passing out in the stools, give to them an inky black colour which sometimes alarms patients. In small doses they usually have an astringent action, and tend to cause constipation. Larger doses, on the other hand, seem to stimulate peristalsis, and increase the number of stools, and sometimes even small doses will cause diarrhœa in some individuals. After absorption into the **blood** they are found to increase, not only the number of the blood-corpuscles, but the percentage of hæmoglobin contained in them, and may also cause a little free iron to be present in the serum. By thus increasing oxidation in the **tissues** they increase the functional activity of the various organs. The effect of ferrous and ferric salts added to the blood is very different, ferric salts producing a firm coagulum, whereas the ferrous salts tend rather to diminish the coagulability of the blood.

Iron has an action on the **nervous system** which varies according to the dose and mode of administration. When injected subcutaneously in **frogs,** iron salts cause slight excitement and then paralysis of the central nervous system. In the later stages of poisoning the irritability of the voluntary muscles is diminished,

[1] Preyer, *Die Blutcrystalle.* Jena, 1871.

but the heart is not affected. In mammals they cause congestion of the stomach and intestine, and **diarrhœa**. They produce **paralysis** both of sensation and motion. The **blood-pressure** falls. This is due to paralysis of the **vaso-motor nerves**, especially of the intestine, resembling that produced by arsenic, antimony, emetin, and colchicin.

Iron is **eliminated** to a considerable extent by the bile (p. 405), by the mucous membrane of the intestine, and by the kidneys.

Uses of Iron.—The ferrous salts are rarely employed for their local action. The ferric salts are used as **styptics**. The strong solution of perchloride may be employed to arrest bleeding from the cavity of a tooth after extraction, or to stop the oozing from a wound where it is impossible to ligature all the bleeding points. When diluted it may be used as an injection to arrest hæmorrhage from the nose, or may be injected into the cavity of the uterus to arrest bleeding from that organ. Mixed with laudanum it has been used as an injection in gonorrhœa and gleet. Both ferrous and ferric salts are administered internally in order to produce the general action of iron in increasing the blood-corpuscles. They differ to some extent, however, the ferrous salts having a less astringent action on the intestines than the ferric. In cases where the mucous membrane of the alimentary canal is irritable this is advantageous, as in such instances the ferric salts might cause digestive disturbances and headache. In other instances, however, especially those where the tongue is pale and flabby, the more astringent preparations are to be preferred. The chief use of iron is as a **hæmatinic**, and the condition in which it is most beneficial is where we have anæmia and chlorosis, whether these be due to loss of blood, imperfect nutrition, chronic discharges, scrofula, syphilis, malarial poisoning, amenorrhœa or albuminuria, or be consequent upon acute febrile disease; but it is also serviceable in a number of disturbances of the nutritive and nervous systems. It has been recommended in large doses in cases of blood-poisoning, such as diphtheria and erysipelas, and in nervous diseases like chorea, epilepsy, giddiness, formication, twitching of the fingers, and subjective sensations of light and heat or cold to which some patients are liable, especially about the climacteric period. It is also used internally in order to diminish discharges from the mucous membranes of the intestines, as in chronic diarrhœa and dysentery, and from the vagina in leucorrhœa. It acts as an astringent on the kidney, lessening the amount of blood in hæmaturia, and sometimes the amount of albumen in albuminuria. It is also a useful adjunct to diuretics in cardiac and renal dropsy (p. 338).

B.P. Vinum Ferri.—This is prepared by macerating iron wire in sherry for a month. Some of it is converted into tartrate and dissolved by the bitartrate of potassium in the wine.

Dose.—1 to 2 fl. dr. or more.

Use.—It is useful in anæmia both in children and adults, and may be given with cod-liver oil.

B.P. Mistura Ferri Aromatica.—This is a curious preparation containing tannate of iron in very small quantities. It is sometimes called Heberden's ink. It is usually said that iron and tannin are incompatible, and so they are in so far that they produce ink, but this preparation is said to be a very useful one.

Iron cannot be taken up in very large quantities, and its absorption is often prevented by the condition of the patient's stomach. This preparation has been put together evidently with the view of combining all the drugs which were likely to do good by themselves, and in total disregard of the chemical action which would take place among themselves.

Preparation.—By macerating pale cinchona bark (1 oz.), calumba root ($\frac{1}{2}$-oz.), cloves ($\frac{1}{4}$-oz.), and fine iron wire ($\frac{1}{2}$-oz.), in peppermint water (12 oz.) for three days, agitating occasionally; then filtering and adding as much peppermint water to the filtrate as will make the product measure $12\frac{1}{2}$ fl. oz.; to this add compound tincture of cardamoms (3 fl. oz.) and tincture of orange peel ($\frac{1}{2}$ fl. oz.), and preserve the mixture in a well-stopped bottle. The pale cinchona bark contains tannin, which combines with the iron. Both it and calumba are gastric tonics, and the carminatives relieve flatulence.

Dose.—1 to 2 fl. oz.

Ferri Sulphas, B. and U.S.P. Sulphate of Iron. $FeSO_4.7H_2O$; 277·9.

Characters.—In oblique rhombic prisms, of a pale greenish blue colour and styptic taste.

Solubility.—It is insoluble in rectified spirit, soluble in water.

Reactions.—The aqueous solution gives the reaction of a sulphate (p. 594) and of a ferrous salt (p. 736).

Dose.—1 to 5 grains.

Preparations.

B.P.	U.S.P.
Ferri Sulphas Exsiccata............	Ferri Sulphas Exsiccata.
Pilula Aloes et Ferri (*vide* p. 522) 1 part in 7.	

Ferri Sulphas Exsiccata, B.P.; Ferri Sulphas Exsiccatus, U.S.P. Dried Sulphate of Iron. $FeSO_4.H_2O$; 169·9.

Prepared by heating sulphate. It is less apt to oxidise, and is well fitted for pills.

Dose.—$\frac{1}{2}$ to 3 grains.

Preparation.

U.S.P.

Pilulæ Aloes et Ferri (*vide* p. 523).

Ferri Sulphas Granulata, B.P.; Ferri Sulphas Præcipitatus, U.S.P. Granulated Sulphate of Iron, B.P. Precipitated Sulphate of Iron, U.S.P. $FeSO_4.7H_2O$; 277·9.

Characters and Tests.—In small granular crystals of a pale

greenish-blue colour. In other respects it corresponds to the characters and tests for sulphate of iron.

DOSE.—1 to 5 grains.

USES.—It is very **astringent**. It has been used externally as ointment or lotion to the skin in erysipelas, as a lotion in ophthalmia, and as a lotion or injection in prolapsus ani, and bleeding piles. It has also been used as an injection in gonorrhœa and leucorrhœa.

Internally it is used in cases of anæmia, especially where this is accompanied by a tendency to profuse sweating, passive hæmorrhages, or mucous discharges, such as chronic catarrh or leucorrhœa. Its astringent action on the stomach has been said to render it serviceable in gastrodynia and gastric ulcer.

Ferri Carbonas Saccharata, B.P.; Saccharatus, U.S.P. SACCHARATED CARBONATE OF IRON, B.P.; SACCHARATED FERROUS CARBONATE, U.S.P.

Carbonate of iron, FeO,CO_2 or $FeCO_3$, mixed with peroxide of iron and sugar, the carbonate forming at least 37 per cent. of the mixture B.P., 15 per cent. U.S.P.

CHARACTERS.—Small coherent lumps, or powder, of a grey colour, with a sweet, very feeble chalybeate taste.

SOLUBILITY.—It dissolves with effervescence (carbonate) in warm hydrochloric acid diluted with half its volume of water.

REACTIONS.—The solution gives only traces of sulphate (p. 595) and exhibits the reactions of a ferrous salt.

DOSE.—5 to 20 grains.

PREPARATIONS.

B.P.		DOSE.
Pilula Ferri Carbonatis (*vide* p. 522)	1 part in $1\frac{1}{4}$	5–20 grs.
U.S.P.		
Massa Ferri Carbonatis		3–5 grs.

U.S.P. Massa Ferri Carbonatis. MASS OF CARBONATE OF IRON.—Sulphate of iron, 100 parts; carbonate of sodium, 110 parts; honey, 38 parts; sugar, 25 parts; syrup and water, q.s.

Mistura Ferri Composita, B. and U.S.P. COMPOUND MIXTURE OF IRON. GRIFFITH'S MIXTURE.

COMPOSITION.—Sulphate of iron, 25 grs.; carbonate of potassium, 30 grs.; myrrh and refined sugar, of each 60 grs.; spirit of nutmeg, 4 fl. drs.; rose water, $9\frac{1}{2}$ fl. oz., B.P. Sulphate of iron, 6; myrrh, 18; sugar, 18; carbonate of potassium, 8; spirit of lavender, 50; rose water, 900, U.S.P.

DOSE.—1 to 2 fluid ounces.

USES.—Carbonate of iron in its various preparations is one of the most useful forms of iron for administration as a **hematinic** and **emmenagogue**.

Liquor Ferri Persulphatis, B.P.; Tersulphatis, U.S.P. SOLUTION OF PERSULPHATE OF IRON, B.P.; OF TERSULPHATE, U.S.P. $Fe_2(SO_4)_3$; 399·8.

CHARACTERS.—A dense solution of a dark-red colour, inodorous and very astringent, miscible in all proportions with alcohol and water.

REACTIONS.—Diluted with ten volumes of water, it gives the reactions of a sulphate and of a ferric salt only.

PREPARATIONS IN WHICH SOLUTION OF PERSULPHATE OF IRON IS USED.

B.P.	U.S.P.
Ferri et Ammonii Citras.	Ferri et Ammonii Citras.
Ferri et Quininæ Citras.	" " " Tartras.
Ferri Peroxidum Hydratum.	" " Potassii "
Ferrum Tartaratum.	" Oxidum Hydratum.
	" " " cum Magnesiâ.
	Liquor Ferri Nitratis.
	" " Citratis.

USES.—Not used as a remedy, but to prepare peroxide, &c.

U.S.P. Liquor Ferri Subsulphatis. SOLUTION OF SUBSULPHATE OF IRON. SOLUTION OF BASIC FERRIC SULPHATE. (MONSEL'S SOLUTION.)

CHARACTERS. — Like the tersulphate; but on mixing two volumes of the solution with one of concentrated sulphuric acid a solid white mass separates on standing.

DOSE.—3 to 10 minims (·18–·64 c.c.).

ACTION.—**Astringent, styptic, hæmatinic.** Less irritating than the tersulphate.

USES.—Like the chloride. It is a useful astringent in relaxed sore-throat and tonsillitis.

U.S.P. Ferri Oxidum Hydratum. HYDRATED OXIDE OF IRON. $Fe_2(HO)_6$; 213·8.

CHARACTERS.—A soft, moist, pasty mass, of a reddish-brown colour.

SOLUBILITY.—Dissolves readily in diluted hydrochloric acid.

REACTIONS.—The solution gives the reaction of a ferric salt only.

DOSE.—$\frac{1}{4}$ to $\frac{1}{2}$ ounce.

USE.—As an **antidote** for arsenic, it should be given in doses of a tablespoonful every five or ten minutes. It may be used in anæmia and amenorrhœa.

PREPARATIONS.

U.S.P. Emplastrum Ferri (hydrated oxide dried, with Canada turpentine, Burgundy pitch, and lead plaster).

U.S.P. Trochisci Ferri (troches of iron). Iron lozenges, 5 grs. in each lozenge.

U.S.P. Ferri Oxidum Hydratum cum Magnesiâ. HYDRATED OXIDE OF IRON WITH MAGNESIA.—Antidote to arsenious acid.

PREPARATION.—Mix the solution of tersulphate of iron 1,000 grs. (65·00 gm.) with twice its weight of water. Rub the magnesia, 150 grains (10·00 gm.) with water to a smooth and thin mixture; transfer this to a bottle capable of holding 32 fl. oz., or about 1 litre, and fill it up with water. When the preparation is wanted for use, mix the two liquids by adding the magnesia mixture gradually to the iron solution, and shake them together until a homogeneous mass results.

NOTE.—The diluted solution of tersulphate of iron and the mixture of magnesia with water should always be kept on hand, ready for immediate use.

USE.—As an antidote in poisoning by arsenic.

B.P. Ferri Peroxidum Hydratum. HYDRATED PEROXIDE OF IRON. $Fe_2O_3H_2O$ or $Fe_2O_2(HO)_2$.

CHARACTERS.—A reddish-brown powder, destitute of taste and not magnetic.

SOLUBILITY.—It dissolves completely, though slowly, with the aid of heat, in hydrochloric acid, diluted with half its volume of water.

REACTIONS.—The solution gives the reactions of a ferric salt only.

DOSE.—5 to 30 grains.

B.P. PREPARATION.

Emplastrum Ferri. IRON PLASTER.—Hydrated peroxide of iron in fine powder, Burgundy pitch, and lead plaster (1 part in 11).

USES.—Not astringent. Given in powder or electuary chiefly in cases of tic and neuralgia.

Iron plaster is often called 'strengthening plaster.' It forms a mechanical support to weak parts and keeps them warm. Used in pains or weakness across the loins in females, in rheumatic pains, as lumbago, weak joints, &c.

Ferrum Redactum, B. and U.S.P. REDUCED IRON.—Metallic iron, with a variable amount of magnetic oxide of iron.

CHARACTERS.—A fine greyish-black powder, strongly attracted by the magnet, and exhibiting metallic streaks when rubbed with firm pressure in a mortar.

SOLUBILITY.—It dissolves in hydrochloric acid with the evolution of hydrogen. ($Fe + 2HCl = Fe\,Cl_2 + H_2$.)

REACTIONS.—The solution gives a light blue precipitate with the yellow prussiate of potash.

IMPURITY.—Magnetic oxide.

TEST.—When ten grains are added to an aqueous solution of fifty grains of iodine and fifty grains of iodide of potassium ($Fe + I_2 = Fe\,I_2$ which dissolves in KI), and digested in a small flask at a gentle heat, the reduced iron is converted into iodide and dissolved, and not more than five grains should be left undissolved, which should be entirely soluble in hydrochloric acid (oxide).

DOSE.—1 to 5 grains.

Trochisci Ferri Redacti, B.P. REDUCED IRON LOZENGES, B.P.—Each lozenge contains one grain of reduced iron.

DOSE.—1 to 6 lozenges.

USES.—This preparation is generally well borne even if the stomach be somewhat irritable. It has no astringent action. When dissolved by the gastric juice it evolves hydrogen, and if sulphur be present as an impurity eructations of sulphuretted hydrogen are produced.

U.S.P. Liquor Ferri Acetatis. SOLUTION OF ACETATE OF IRON.—An aqueous solution of ferric acetate [$Fe_2(C_2H_3O_2)_6$; 465·8]—containing 33 per cent. of the anhydrous salt. Sp. gr. 1·160.

PREPARATION.

Tinctura Ferri Acetatis (Solution of Acetate 50, Alcohol 30, Acetic Ether 2).

DOSE.—15 min. to 1 fl. dr.

B.P. Liquor Ferri Acetatis Fortior. STRONG SOLUTION OF ACETATE OF IRON.

CHARACTERS.—A deep-red fluid with a sour, styptic taste and acetous odour, miscible with water or rectified spirit in all proportions. Sp. gr. 1·127.

REACTIONS.—Diluted with water it gives the reactions of a ferric salt.

DOSE.—1 to 8 minims.

PREPARATIONS.

B.P.		DOSE.
Liquor Ferri Acetatis	(strong solution 1, diluted with water to 4)	5 to 30 min.
Tinctura Ferri Acetatis	(„ „ 1, „ „ spirit to 4)	5 to 30 min.

USE.—May be given along with acetate of potassium in dropsy.

U.S.P. Mistura Ferri et Ammonii Acetatis. MIXTURE OF ACETATE OF IRON AND AMMONIUM (BASHAM'S MIXTURE) comprises tincture of chloride of iron (2 parts), diluted acetic acid (3), solution of acetate of ammonium (20), elixir of orange (10), syrup (15), water (50).

DOSE.—$\frac{1}{2}$–1 fluid ounce.

USE.—As a hæmatinic generally, and in cases of renal disease especially.

U.S.P. Ferri Chloridum. CHLORIDE OF IRON. $Fe_2Cl_6.12H_2O$; 540·2.

CHARACTERS.—Orange-yellow crystalline masses, very deliquescent, odourless or having a faint odour of hydrochloric acid, a styptic taste, and an acid reaction.

SOLUBILITY.—Freely and wholly soluble in water, alcohol, or ether.

REACTIONS.—The dilute aqueous solution gives a brown-red precipitate with water of ammonia, a blue one with test solution of ferrocyanide of potassium, and a white one, insoluble in nitric acid, with test solution of nitrate of silver.

USES.—In the solid state it keeps indefinitely, whereas in solution it is apt to deposit ferric oxide leaving excess of acid in the solution which renders it irritating. When required it may be dissolved in water in the proportion of 1$\frac{1}{2}$–6 drachms to the ounce of water. When semi-deliquesced it is an efficient styptic.

Liquor Ferri Perchloridi Fortior, B.P. Liquor Ferri Chloridi, U.S.P. STRONG SOLUTION OF PERCHLORIDE OF IRON, B.P. SOLUTION OF CHLORIDE OF IRON, U.S.P.

CHARACTERS.—An orange-brown solution with a strong styptic taste, miscible with water and rectified spirit in all proportions.

REACTIONS.—Diluted with water it gives the reactions of a chloride (p. 594) and of a ferric salt only.

PREPARATIONS.

B.P.		DOSE.
Liquor Ferri Perchloridi	(with water)......1 volume in 4...	10–30 min.
Tinctura Ferri Perchloridi	(with spirit)...1 volume in 4...	10–30 min.

U.S.P. Tinctura Ferri Chloridi. TINCTURE OF CHLORIDE OF IRON. Dose, 10 to 30 minims.

PREPARATION.

Mistura Ferri et Ammonii Acetatis, U.S.P.

USES.—The strong solution is one of the most powerful **styptics** we possess. It forms, almost immediately, a hard black coagulum with blood, and by blocking up the mouths of the vessels arrests further hæmorrhage. Cotton wool steeped in this may be used to arrest the hæmorrhage from the cavity of a tooth after its extraction, and to stop the bleeding from leech-bites. It has been applied as a caustic in hospital gangrene, in bleeding from the uterus, and, diluted with three volumes of water, it may be injected into the uterine cavity, but is better applied by swabbing it over the interior of the uterus with a sponge. It has been injected into aneurisms, in order to produce coagulation within them. There is, however, great danger that part of the clot may become detached and carried onwards, producing embolism, or that inflammation and ulceration may take place within the aneurismal sac itself.

It has also been injected into varicose veins and nævi for a similar purpose, but in nævi on the face it may cause sloughing, and leave scars. It has been used as a spray for the purpose of arresting hæmorrhage from the lungs.

The liquor and tincture are perhaps more often employed than any other preparation of iron. They are **astringent**, generally causing constipation, but sometimes they irritate the intestine, increasing the number of stools. They are amongst the most efficient preparations of iron as **hæmatinics**. They are contraindicated by a red irritable tongue, and succeed best when the tongue is pale, flabby, and marked with the teeth at the edges.

I have found that when patients bear iron badly and complain of headache even after small doses, they can take with benefit a single drop of the tincture or solution of the perchloride in a full tumbler of water. In its great dilution the mixture somewhat resembles chalybeate waters, which often succeed much better than pharmaceutical preparations. The tincture has been given in erysipelas in very large doses, 20–30 minims, repeated every hour or two.

The tincture is useful in purpura with extensive extravasations. In skin-diseases generally, such as eczema, lupus, seborrhœa, and psoriasis, it is only useful when they are associated with anæmia.

B.P. Liquor Ferri Dialysatus. SOLUTION OF DIALYSED IRON.—This solution of dialysed iron, so-called, is a solution of highly basic ferric oxychloride, or chloroxide of iron, from which most of the acidulous matter has been removed by dialysis.

CHARACTERS.—A clear dark reddish-brown liquid, free from

any marked ferruginous taste. Neutral to test-papers. Specific gravity about 1·407.

Reactions.—The solution gives no precipitate with ferrocyanide of potassium or with nitrate of silver, but after being heated with hydrochloric acid it yields with ferrocyanide of potassium a blue precipitate.

Dose.—10 to 30 minims.

Liquor Ferri Pernitratis, B.P.; Liquor Ferri Nitratis U.S.P. Solution of Pernitrate of Iron, B.P.; Nitrate of Iron, U.S.P. $Fe_2(NO_3)_6$; 483·8.

Characters.—A clear solution of a reddish-brown colour, slightly acid and astringent to the taste.

Reactions.—When to a little of it placed in a test-tube half its volume of pure sulphuric acid is added, and then a solution of sulphate of iron is poured on, the whole assumes a dark-brown colour (nitrate). It gives the reactions of a ferric salt only.

Dose.—10 to 40 minims.

Uses.—It has been used as an **astringent** in the diarrhœa of children, and, also as an astringent, to diminish discharges from mucous surfaces, also to arrest hæmorrhage from internal organs. It can be given along with spirit of nitrous ether or nitrate of potassium in cases of anæmia with albuminuria and dropsy.

Ferrum Tartaratum, B.P.; Ferri et Potassii Tartras, U.S.P. Tartarated Iron, B.P.; Tartrate of Iron and Potassium, U.S.P.

Characters.—Thin, transparent scales of a deep garnet colour, slightly sweetish and astringent in taste.

Solubility.—It is soluble in water and sparingly soluble in spirit.

Reactions.—The aqueous solution, when acidulated with hydrochloric acid, gives the reactions of a ferric salt only. When the salt is boiled with solution of soda, peroxide of iron separates, but no ammonia is evolved (not the ammonia-citrate), and the filtered solution when slightly acidulated by acetic acid gives, as it cools, a crystalline deposit (potassium).

Dose.—5 to 10 grains.

The double salts of iron with potassium, ammonium, quinine, &c., are usually called the **scale preparations of iron** from their appearance. These are less astringent than, and do not confine the bowels so much as, either the proto-sulphate or the per-salts. Another advantage is that they may be given along with alkaline carbonates without being precipitated. They are employed in cases where the other preparations cause headache, or derange the digestion, on account of the stomach being irritable.

U.S.P. Ferri et Ammonii Tartras. Tartrate of Iron and Ammonium.

Characters.—Transparent scales, varying in colour from garnet-red to yellowish-brown, only slightly deliquescent, without

odour, having a sweetish and slightly ferruginous taste and a neutral reaction.

SOLUBILITY.—It is readily soluble in water.

REACTIONS.—It is not precipitated by ammonia, but gives a brown precipitate of ferric oxide with potash and evolves the vapour of ammonia. On adding test solution of ferrocyanide of potassium to the salt, no blue colour or precipitate is produced unless the solution is acidulated with hydrochloric acid.

Ferri et Ammonii Citras, B. and U.S.P. CITRATE OF IRON AND AMMONIUM.

CHARACTERS.—In thin, transparent scales of a deep red colour, slightly sweetish and astringent in taste. It feebly reddens litmus paper.

SOLUBILITY.—It is soluble in water, but almost insoluble in rectified spirit.

REACTIONS.—Heated with solution of potash it evolves ammonia and deposits peroxide of iron. The alkaline solution from which the iron has separated does not, when slightly supersaturated with acetic acid, give any crystalline deposit (distinction from and absence of tartrate).

DOSE.—5 to 10 grains.

PREPARATIONS.

B.P.		DOSE.
Vinum Ferri Citratis.	8 grains in 1 fl. oz. of orange wine...	1–4 fl. drs.
U.S.P.		
Ferri et Strychninæ Citras..		
Liquor Ferri et Quininæ Citratis		
Vinum Ferri Citratis		1–2 fl. drs.

U.S.P. Vinum Ferri Citratis. (Citrate of iron and ammonium, 4; tincture of sweet orange-peel, 12; syrup, 36; stronger white wine, 44.)

U.S.P. Liquor Ferri Citratis. AN AQUEOUS SOLUTION OF FERRIC CITRATE, $Fe_2(C_6H_5O_7)_2$; 489·8, containing about 35 per cent. of the anhydrous salt.

CHARACTERS.—A dark brown liquid, odourless, having a slightly ferruginous taste and acid reaction.

REACTIONS.—It gives the reactions of a citrate (p. 594) and a bluish green precipitate with ferrocyanide of potassium, which is increased and rendered dark blue by the subsequent addition of hydrochloric acid.

DOSE.—Ten minims (0·6 c.c.), equal to 5 grains of the salt.

U.S.P. Ferri Citras. CITRATE OF IRON. $Fe_2(C_6H_5O_7)_2.6H_2O$; 597·8.

CHARACTERS.—Transparent garnet-red scales, permanent in the air, odourless, having a very faint ferruginous taste and an acid reaction.

SOLUBILITY.—Slowly but completely soluble in cold water and readily so in boiling water; insoluble in alcohol.

REACTIONS.—*Vide* supra.

PREPARATION.

Ferri Quininæ Citras.

USE.—Is pleasant. A solution of 240 grains in 1 fl. oz. of

water keeps perfectly, and may be given in doses of 10 minims, equal to 5 grains, as a tonic.

Ferri et Quininæ Citras, B. and U.S.P. CITRATE OF IRON AND QUININE.

CHARACTERS.—Thin scales of a greenish golden-yellow colour, somewhat deliquescent.

SOLUBILITY.—It is entirely soluble in cold water.

REACTIONS.—The solution is very slightly acid, and is precipitated reddish-brown (iron) by solution of soda, white (quinine) by solution of ammonia, blue by the yellow (ferric) and red prussiates (ferrous) of potash, and greyish-black by tannic acid. The taste is bitter (quinine) as well as chalybeate.

DOSE.—5 to 10 grains.

U.S.P. Liquor Ferri et Quininæ Citratis. SOLUTION OF CITRATE OF IRON AND QUININE. (Citrate of iron and ammonium, 65; quinine, 12; citric acid, 28; alcohol, 30; distilled water up to 200.)

DOSE.—8 to 15 minims ($\frac{1}{2}$–1 c.c.).

PREPARATION.

U.S.P.

Vinum Ferri Amarum. BITTER WINE OF IRON. (Solution of citrate of iron and quinine, 8; tincture of sweet orange peel, 12; syrup, 36; stronger white wine, 34.) Dose 1–2 fl. drs. (4–16 c.c.).

U.S.P. Ferri et Strychninæ Citras. CITRATE OF IRON AND STRYCHNINE.

CHARACTERS.—Transparent garnet-red scales, deliquescent on exposure to air; odourless, having a bitter and slightly ferruginous taste and a slightly acid reaction.

SOLUBILITY.—Soluble in water.

REACTIONS.—If one gm. of the salt be dissolved in 4 c.c. of water in a small test-tube, then 1 c.c. of solution of potassa added and the mixture shaken with 2 c.c. of chloroform, the residue left on evaporating the chloroform will answer to the reaction of strychnine. (See 'Strychnina.')

DOSE.—3 to 5 grains (0·20—0·33 gm.).

USES.—As **tonic** and chalybeate to combine the uses of strychnine and iron.

U.S.P. Ferri et Ammonii Sulphas. SULPHATE OF IRON AND AMMONIUM. AMMONIO-FERRIC SULPHATE OR AMMONIO-FERRIC ALUM. $Fe_2(NH_4)_2(SO_4)_4.24H_2O$; 963·8.

This is an ammonia iron-alum in which the place of the aluminium oxide is occupied by the ferric oxide.

CHARACTERS.—Pale violet octahedral crystals efflorescent on exposure to air, odourless, having an acid styptic taste and a slightly acid reaction.

DOSE.—5 to 10 grains.

USES.—It is more **astringent** than common alum, and has not the stimulating properties of other iron salts. It is useful in

leucorrhœa. Internally it is sometimes very useful in lessening albumen in cases of intermittent albuminuria.

U.S.P. Ferri Lactas. LACTATE OF IRON. $Fe(C_3H_5O_3)_2.3H_2O$; 287·9.

CHARACTERS.—Pale greenish-white, crystalline crusts or grains, permanent in the air; odourless, having a mild sweetish ferruginous taste and a slightly acid reaction.

SOLUBILITY.—Soluble in water.

REACTIONS.—When heated on platinum foil the salt froths up, gives out thick white acrid fumes, and chars, a brown-red residue being finally left. If the salt be boiled for fifteen minutes with nitric acid of the sp. gr. 1·200, white granular mucic acid will be deposited on cooling the liquid.

PREPARATION.

U.S.P. Syrupus Hypophosphitum cum Ferro. (Lactate of iron, 1; syrup of hypophosphites, 99.)

DOSE.—12–20 grains per diem; of syrup, ½ to 1 fl. dr.

USE.—In chlorosis and anæmia.

U.S.P. Ferri Oxalas. OXALATE OF IRON. $FeC_2O_4.H_2O$; 161·9.

CHARACTERS.—A pale yellow, or lemon-yellow crystalline powder, permanent in the air, odourless and nearly tasteless.

SOLUBILITY.—It is very slightly soluble in cold or hot water, but soluble in cold concentrated hydrochloric acid and in hot diluted sulphuric acid.

DOSE.—2 to 3 grains (0·13 to 0·20 gm.).

B. and U.S.P. Syrupus Ferri Iodidi. SYRUP OF IODIDE OF IRON. FeI_2; 309·1.—It contains 4·3 grains of iodide of iron in 1 fluid drachm.

CHARACTERS.—Yellowish or greenish-yellow liquid with a sweet inky taste.

DOSE.—½ to 1 fl. dr.

B. and U.S.P. Pilula Ferri Iodidi (*vide* pp. 522, 523). PILL OF IODIDE OF IRON. Pill with sweet inky taste.

DOSE.—3 to 8 grains.

U.S.P. Ferri Iodidum Saccharatum. SACCHARATED IODIDE OF IRON.

CHARACTERS.—A yellowish-white or greyish powder very hygroscopic, odourless, having a sweetish ferruginous taste, and a slightly acid reaction.

DOSE.—2 to 5 grains (0·13–0·33 gm.).

USES.—Iodide of iron is given when a combination of the effect of iodine on the lymphatic system is desired along with the hæmatinic action of iron. It is thus very useful in the form of the syrup in dispensary practice in large towns, where pale, anæmic, flabby, and scrofulous children abound, and come in large numbers to be treated. It is generally advantageous to combine

it with cod-liver oil, a few drops of the syrup being dropped into the oil and taken along with it. It has been given in phthisis in the same way, and has been found useful in rheumatic arthritis and syphilis.

U.S.P. Syrupus Ferri Bromidi. SYRUP OF BROMIDE OF IRON.—A syrupy liquid containing 10 per cent. of ferrous bromide. $FeBr_2$; 215·5.

DOSE.—$\frac{1}{2}$ to 1 fluid drachm (1·9 to 3·75 c.c.).

USE.—In nervous diseases accompanied by anæmia. It is doubtful, however, whether it is not better to give the iron and bromine separately, as sufficient bromine cannot be given in this form. It may, however, be advantageously combined with other bromides.

B.P. Ferri Arsenias. ARSENIATE OF IRON.—Arseniate of iron, $Fe_3As_2O_8$, partially oxidised.

CHARACTERS.—A tasteless amorphous powder of a green colour.

SOLUBILITY.—It is insoluble in water, but readily dissolved by hydrochloric acid.

REACTIONS.—The solution in hydrochloric acid gives a copious light-blue precipitate with the yellow prussiate of potash (ferric), and a still more abundant one of a deeper colour with the red prussiate of potash (ferrous). A small quantity boiled with an excess of caustic soda and filtered gives, when exactly neutralised by nitric acid, a brick-red precipitate on the addition of solution of nitrate of silver (arseniate).

DOSE.—$\frac{1}{16}$ to $\frac{1}{2}$ grain.

USES.—Used when we wish to employ arsenic and iron together, as in skin-diseases in anæmic subjects.

Ferri Phosphas, B. and U.S.P. PHOSPHATE OF IRON.—Phosphate of iron, $Fe_3P_2O_8$, partially oxidated.

CHARACTERS.—A slate-blue amorphous powder.

SOLUBILITY.—It is insoluble in water, soluble in hydrochloric acid.

REACTIONS.—The solution yields a precipitate with both the yellow (ferric) and red prussiates of potash, that afforded by the latter being the more abundant (ferrous); and when treated with tartaric acid and an excess of ammonia, and subsequently with the solution of ammonio-sulphate of magnesium, lets fall a crystalline precipitate (phosphate). When the salt is digested in hydrochloric acid with a lamina of pure copper, a dark deposit does not form on the metal (distinction from and absence of arseniate).

DOSE.—5 to 10 grains.

PREPARATIONS CONTAINING PHOSPHATE OF IRON.

B.P.	DOSE.
Syrupus Ferri Phosphatis (freshly-precipitated phosphate (p. 738) is dissolved in dilute phosphoric acid and sugar added) 1 gr. in 1 fl. dr.	...1 fl. dr.

U.S.P.

Syrupus Ferri, Quininæ, et Strychninæ Phosphatum. (Phosphate of iron, 133; quinine, 133; strychnine, 4; phosphoric acid, 800; sugar, 6,000; distilled water up to 10,000.) This preparation resembles Easton's Syrup.

USES.—It is used in diabetes, in rickets, and in nervous depression. It is frequently given along with the phosphates of calcium, potassium, and sodium, as the preparation usually called Parrish's Chemical Food, or with the phosphates of quinine and strychnine, as in Easton's Syrup.

U.S.P. Ferri Pyrophosphas. PYROPHOSPHATE OF IRON.

CHARACTERS.—Thin, apple-green, transparent scales, permanent in dry air when excluded from light, but turning dark on exposure to light. Odourless, having an acidulous, slightly saline taste, and a slightly acid reaction.

SOLUBILITY.—Very soluble in water.

REACTIONS.—When heated with solution of potassa in excess a brown-red precipitate is thrown down, and the filtrate, after being supersaturated with acetic acid, yields a white precipitate with test solution of nitrate of silver (difference from phosphates).

DOSE.—2 to 5 gr. (0·13 to 0·33 gm.).

USES.—Has no disagreeable taste, and is very soluble, so that it can be given in any form.

U.S.P. Ferri Hypophosphis. HYPOPHOSPHITE OF IRON.—$Fe_2(H_2PO_2)_6$; 501·8.

CHARACTERS.—A white or greyish-white powder, permanent in the air, odourless and nearly tasteless.

SOLUBILITY.—It is only slightly soluble in water, more readily so in presence of hypophosphorous acid, freely soluble in hydrochloric acid, or in solution of citrate of sodium, forming with the latter a green solution.

REACTIONS.—When strongly heated in a dry test-tube, the salt evolves a spontaneously inflammable gas (phosphoretted hydrogen), and on ignition leaves behind ferric pyrophosphate. The salt is readily oxidised by nitric acid or other oxidising agents. It should be completely soluble in acetic acid (absence of ferric phosphate). This solution, when mixed with test-solution of oxalate of ammonium, should not afford a white precipitate soluble in hydrochloric acid (absence of calcium).

DOSE.—5 to 10 grains in pill, more generally given in syrup.

USES.—In nervous debility with anæmia, and also in phthisis.

U.S.P. Ferri Valerianas. VALERIANATE OF IRON.—$Fe_2(C_5H_9O_2)$; 717·8.

CHARACTERS.—A dark tile-red amorphous powder, permanent in dry air, having a faint odour of valerianic acid, and a mildly styptic taste.

SOLUBILITY.—Insoluble in cold water, but readily soluble in alcohol.

REACTIONS.—Boiling water decomposes it, setting free the valerianic acid and leaving ferric hydrate. When slowly heated the salt parts with its acid without fusing, but when rapidly heated it fuses and gives off inflammable vapours having the odour of butyric acid.

DOSE.—1 grain or more.

USES.—In hysteria with anæmia.

MANGANESE. Mn; 55.

Manganesii Oxidum Nigrum, B.P.; Mangani Oxidum Nigrum, U.S.P. BLACK OXIDE OF MANGANESE.—Native crude peroxide of manganese containing at least 66 of the pure oxide. MnO_2; 86, U.S.P.

CHARACTERS.—A heavy black powder.

SOLUBILITY AND REACTIONS.—Dissolves almost entirely in hydrochloric acid with evolution of chlorine, and gives off oxygen when heated to redness.

USES.—Used for producing chlorine, and for making oxygen. It has been used instead of bismuth in pyrosis and irritable conditions of the stomach, with pain after eating; and instead of iron in debilitating diseases, anæmia, syphilis, scurvy, and in skin-diseases.

U.S.P. Mangani Sulphas. SULPHATE OF MANGANESE.—$MnSO_4.4H_2O$; 222.

CHARACTERS.—Colourless or pale rose-coloured, transparent right rhombic prisms, odourless, having a slightly bitter and astringent taste, and a faintly acid reaction.

SOLUBILITY.—Soluble in water.

REACTIONS.—The aqueous solution of the salt yields, with sulphide of ammonium, a flesh-coloured precipitate completely soluble in moderately diluted acetic acid (absence of zinc); with test-solution of ferro-cyanide of potassium it affords a reddish-white precipitate, and a brown one with test-solution of ferricyanide of potassium.

ACTION OF MANGANESE SALTS.—When injected into the blood, or subcutaneously, manganese salts **paralyse** voluntary movement and reflex action, and stop the **heart** in diastole. The paralysis of reflex action is due to destruction of the transverse conduction of the **spinal cord** (p. 161), longitudinal conduction remaining intact until death (Kobert). Proto-sulphate produces purging in doses of 1 to 2 drms., and, in consequence of Gmelin's experiments, has been thought to increase the secretion of bile.

USES.—Has been used in place of iron in anæmia, but without good results. Possibly it may be serviceable in amenorrhœa.

Potassii Permanganas, B.P. and U.S.P.—*Vide* p. 614.

Class VIII.

GROUP II.—GOLD, PLATINUM.

AURUM; GOLD. Au; 196·2.

B.P. Gold, Fine. GOLD, FREE FROM METALLIC IMPURITIES.

Gold foil is used for stopping teeth and to make the test solution.

B.P. Solution of Chloride of Gold.

PREPARATION.—By dissolving gold foil in a mixture of nitric and hydrochloric acids and diluting.

U.S.P. Auri et Sodii Chloridum. CHLORIDE OF GOLD AND SODIUM.

A mixture composed of equal parts of dry chloride of gold, $AuCl_3$; 302·4; and chloride of sodium, NaCl; 58·4.

CHARACTERS.—An orange-yellow powder, slightly deliquescent in damp air, odourless, having a saline and metallic taste and a slightly acid reaction.

SOLUBILITY.—The compound is very soluble in water; at least one half of it should be soluble in cold alcohol.

REACTIONS.—When exposed to a red heat it is decomposed and metallic gold is separated. A fragment of the compound imparts an intense persistent colour to a non-luminous flame.

PREPARATION.—By dissolving gold in nitro-hydrochloric acid and evaporating to dryness, chloride of gold is obtained. This is dissolved in water, and mixed with its own weight of pure decrepitated common salt also dissolved in water. The mixed solution is then evaporated to dryness.

DOSE.—$\frac{1}{10}$ to $\frac{1}{5}$ grain (·006–·012 gm.), once or twice a day.

ACTION.—Salts of gold cause rapid **paralysis** of the central nervous system in frogs, which appears to affect first the optic lobes and cerebellum, then the cord, and lastly the cerebral lobes (*vide* p. 183 *et seq.*). In mammals small doses appear to increase the appetite; larger ones cause symptoms of irritation in the **stomach** and **intestines**, viz. loss of appetite, diarrhœa, and emaciation, followed by paralysis of the limbs, a catarrhal condition of the **respiratory** passages, and death by asphyxia. Large doses injected into the veins cause œdema of the **lungs**, and rapid death, with convulsions, from asphyxia. In man they are said to increase the **secretions**, and to produce salivation like mercury, but without stomatitis. They are **eliminated** in the urine.

USES.—Salts of gold have been supposed to act like those of mercury and silver. They have been given like mercurial salts in syphilis, scrofula, and cancer; and, like silver salts, have been used in myelitis. Gold has been supposed to act specifically on the genital organs, and has been used in chronic uterine inflammation and irritation, and inflammation and neuralgia of the ovaries.

PLATINUM. Pt; 197.

B.P. Platinum Foil.

A heavy whitish metal Sp. gr. 8·921. Withstands considerable heat. The foil is convenient for holding salts of organic acids which it is wished to char.

B.P. Solution of Perchloride of Platinum. $PtCl_4$; 339.

PREPARATION.—By dissolving thin platinum foil in a mixture of nitric acid and hydrochloric acid and diluting.

USES.—Used to distinguish potassium from sodium and to precipitate salts of ammonium, and of compound ammonias, e.g. organic alkaloids.

ACTION.—Soluble salts of platinum are as poisonous as arsenic. In frogs they appear to paralyse the centres for voluntary motion in the cerebral lobes, and irritate the motor centres between them and the cord, so that voluntary motion is diminished, but reflex convulsions occur. The excitability of voluntary muscle is much lessened, that of the heart is not apparently altered. In mammals the most prominent symptom is paralysis of the peripheral ends of the vaso-motor nerves. In consequence of this, diarrhœa, blood in the motions, hyperæmia of the abdominal viscera, and ecchymoses of the mucous membrane of the stomach and intestine and bladder occur.

B.P. Platinum Black.

PREPARATION.—Platinum in a state of minute division, obtained by adding excess of carbonate of sodium and some sugar to solution of perchloride of platinum, and boiling until a black precipitate is formed, which is washed and dried.

ACTION.—Platinum-black appears to have a greater power than even charcoal to condense gases, and especially oxygen, in its pores. By giving the oxygen off again it acts as an oxidising agent.

USE.—To test amylic alcohol by oxidising it into valerianic acid.